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A STUDY OF THE LIPOIDS IN NEURONIC DEGENERATION AND IN AMAUROTIC FAMILY IDIOCY.[1]

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IN this paper the term "lipoid" is not used to indicate any specific fatty compounds or group of compounds, but rather as a general term embracing all these bodies. It is commonly employed in this sense by many authors, while those who have used it in a narrower sense do not agree as to its application, so that any restriction of its meaning in the present instance would lead only to confusion.

The earlier investigators sought to obtain information concerning the fatty components of the nervous system by extracting large masses of tissue with suitable solvents and subsequently attempting to isolate the various solutes, to determine their physical and chemical properties and, in the case of the more complex bodies, to resolve them into their constituents. These methods, though crude and obviously limited in their scope, gave much valuable knowledge, and many classifications of the lipoids have been evolved. McLean [22] for example gives the following grouping of substances met with in an ether or alcohol extract of nervous tissue.

(*a*) Neutral fat and fatty acid.

(*b*) Substances of varying chemical nature having no relation to fat, e.g., cholesterol and certain pigments.

(*c*) Phosphatides, i.e., compounds of fatty acid with nitrogen and phosphorus-containing radicles.

(*d*) Cerebrosides, i.e., compounds of fatty acid with a nitrogen-containing radicle and a carbohydrate.

Later workers found means to demonstrate the lipoids *in situ* and,

[1] The work on which this article is based was conducted during the tenure of the Walter Olyer's Travelling Studentship of the University of Birmingham.

by the use of staining reagents before and after the application of fat solvents to microscopical sections, to identify many. It was along these lines that the work to be described was conducted.

(A) Tract Degeneration.

Literature.

Lorrain Smith [16] showed that by the use of a solution of Nile blue it is possible to distinguish between fatty acid and neutral fat, the former assuming a blue colour while the latter stains pink. Mixtures of these bodies become purple, the exact tint depending on their relative concentration.

Lorrain Smith and Mair [17] pointed out that the method employed by Weigert for staining myelin sheaths may be used in the demonstration of other fatty bodies, according to the duration of the mordanting with potassium bichromate. The nature of these bodies can be surmised to some extent from the period at which they stain with hæmatoxylin. Thus triolein and oleic acid coloured faintly on the fourth day and well from the fifth to the twenty-fourth day. Pure cholesterin did not react, but a mixture of triolein and cholesterin stained faintly after two days and clearly on the third to the twenty-fourth day, while a mixture of oleic acid and cholesterin stained clearly after one and three days, feebly after ten days, and not at all after twenty-four days. The reaction is due to oxidation of the lipoid, and if mordanting be continued until oxidation is complete no staining occurs.

Klotz [14] detected fatty acid in degenerated areas by mordanting with copper acetate and subsequently staining with hæmatoxylin.

Cramer [7] gives the chief reactions of the various lipoids in tabular form as follows:—

	Scharlach	Double refrac.	Osmic acid	Osmic ac. after bichrom.	Solubility in cold		
					Acetone	Alcohol	Chlorof.
True fats ..	+	−	+	+	+	+	+
Cholesterin ..	−	+	+	−	+	+	+
Cholesterin esters	+	+	+	−	−	−	+
Phosphatides ..	−	+	+	−	−	+	+
Cerebrosides ..	−	+	+	−	−	−	+
Cholesterin and Fatty acid mixtures	+	+	+	+	+	+	+

Ciaccio [6] states that by immersion of sections in a saturated solution of zinc acetate the saturated fatty acids are rendered insoluble in alcohol. In sections treated in this manner there remain however,

in addition to the fatty acid, the cerebrosides and the lipochrome pigment. The cerebrosides may be removed with a mixture of methyl alcohol and chloroform in equal parts; the fatty acid may be distinguished from the lipochrome pigment by the fact that it is still soluble in an acidified mixture of alcohol and ether, whereas the lipochrome pigment resists solution in this reagent.

The *lipochrome pigment*, or, as the German writers prefer, the "lipofuchsin" of the nerve cells has long been recognized as a constant constituent of the senile nerve cell and as of frequent occurrence at earlier periods of life in morbid conditions affecting the neuron, while in the cells of a few regions, e.g. the olives, it appears to be a normal component. Obersteiner in 1888 studied its distribution in various nerve cells and pointed out its relation to fat, since when controversy has raged as to its exact nature.

Buscaino [4] considers it to be a saturated phosphatide together with traces of some other acetone-soluble lipoid, probably neutral fat.

Biondi [2] believes that it consists in part of glycerine esters and in part of "lipoid."

Marinesco [19], on the other hand, regards it as a compound of lipoid and protein.

Buscaino showed that in the cerebral vessels of healthy subjects minute globules of neutral fat and non-saturated phosphatides can be seen in association with other lipoids.

In pathological conditions of the nervous system quantities of fatty substances are met with.

Virchow, whose studies formed the groundwork of scientific research in this direction, distinguished between fatty degeneration and fatty infiltration, inasmuch as, in the former, the fat was produced *in situ* from the breaking down of protein, whereas, in the latter, fat merely accumulated in the cell.

Rosenfeld [26], however, finally disposed of this theory by showing that, in animals poisoned with bodies known to give rise to fatty degeneration and fed on a foreign fat, this fat appeared in the damaged cells; that lean animals when given these noxious substances did not show fatty degeneration, and that tissues showing marked fatty change did not necessarily, on analysis, contain an excess of fat, were further evidence of the erroneous nature of Virchow's views. He believed that the fat in fatty degeneration was not produced from the cell protein, and that there was no increased infiltration of fat, but that the fat previously present separated out in visible form.

Fischer and Hooker [9] have advanced the theory that fat in the cell exists normally, not in the form of a chemical compound in the protoplasm, nor yet in osmotic solution, but as an emulsion in a hydrated colloid, the proteins acting as the continuous phase of the emulsion. Petrowsky [23] found 36 to 45 per cent. lipoid in the grey matter of ox-brain and 36 to 71 per cent. in the white matter, while Bischoff's figures for the human cord were of a similar order. Fischer and Hooker regard an emulsion as the only mechanism capable of absorbing so great a proportion, and have shown that when fat is so finely emulsified that refraction effects no longer render visible the individual globules, even on high magnification, it loses its power of staining with Sudan III and scharlach R. Acids, produced locally by the action of toxins on the cell or by post-mortem changes therein, or formed elsewhere by a perverted metabolism, as in diabetes, make the protoplasm swell by increasing its capacity for water. The concentration of the proteins being thus reduced, there is a tendency for the emulsion to break, the fat then separating out in visible and stainable globules. Other cell-proteins when subjected to the influence of acid lose their hydrophilic character, become dehydrated, and still further destroy the emulsion. This they regard as the explanation of fatty degeneration. The appearance produced by swelling of one group of proteins and dehydration of another group is that of cloudy swelling, which, it is well recognized, frequently precedes fatty degeneration. Further, they maintain that the hypothesis which supposes the fat to be derived from some precursor like lecithin cannot be entertained, for analysis shows no diminution in that substance, and the amount of visible fat is often greater than could result from a conversion of the whole of the tissue lecithin.

Marinesco [20], during autolysis of spinal ganglion cells, found a lipoid soluble in ether and chloroform developing within the cell, but Biondi and other observers have found it difficult to produce a lipoid by autolysis *in vitro*.

Laignel-Lavastine and Jonnesco [15] transplanted fragments of the cerebellum of a rat under the skin of the same animal. Twelve to twenty-five hours later the Purkinje cells had vanished, leaving spherical granules of various sizes coloured blue with Nile blue, yellow-brown with neutral red and blue-grey with Weigert-Smith. They suggest that these are cholesterin-esters.

Rachmanow [24] transplanted the cerebrum of the rat in a similar manner, and found that after several days the site of the operation was

marked solely by the presence of numerous cells full of lipoid droplets which stained in part like fatty acid, and in part like glycerin esters. All the cerebral substance had disappeared.

With regard to the phagocytosis of fat, Jakob [11, 12], in secondary degeneration in the central nervous system, distinguished various kinds of cells concerned in the absorption and transportation of degeneration products. The *myeloclasts* of the earliest stages contain fine lipoid granules colouring with Sudan and scharlach, and in part red with Nile blue. The *myelophages* contain more lipoid of a similar nature. Both of these forms of cell are stationary.

The "*Gitterzellen*," which, unlike the preceding, are mobile elements, are subdivided into α, β, and γ types.

The α variety, which appears fifty to eighty days after the injury, contain lipoid drops of uniform size darkening with Marchi, colouring with Sudan and scharlach, but not with Ciaccio's method, and taking a red tint with Nile blue. Their contents are isotropic. The β cells, appearing three to six months after the lesion, show coalescence of their globules which are often limited by a membrane not reacting with Nile blue, but appearing somewhat crystalline. The γ type, which is found six months to a year or more from the date of the original trauma, possesses droplets of uniform calibre becoming violet with Nile blue and darkening with osmic acid.

According to later observations the "Gitterzellen" may contain anisotropic substances and inclusions coloured by Fischer's method.

Alzheimer [1] believes that the products of disintegration are transferred by solution in the lymph to neuroglia cells, which during their migration towards the vessels resolve them into simpler compounds. Finally, they are engulfed by mesodermal cells which complete the preparation for their absorption by the blood-stream.

Lotmar's observations [18] on the stages of degeneration in foci of encephalitis produced in rabbits, show that in the most acute lesions the products of disintegration are liberated in the tissues and transported by the lymph to the vessels where there may be found substances not sufficiently altered to give a fat reaction but staining rather with methylene blue, with eosin or with method 6 of Alzheimer.

Kawamura [13] describes in the granular corpuscles near old hæmorrhages a doubly refracting lipoid coloured red with Nile blue and yellow with Sudan but not with neutral red. It was of crystalline form. Of two recent hæmorrhages only one showed anisotropic material and

he concludes that this appears after the isotropic substance and probably consists of cholesterin-esters and cholesterin.

Roussy and Laroche [27] state that the normal myelin is doubly refractile and stains orange-red with Sudan III and blue or blue-violet with Nile blue. The nerve cells in health contain no anisotropic material, nor do the neuroglial or endothelial cells. The lipochrome pigment is isotropic, which they consider is a point in favour of its supposed lipoid nature. In cerebral softening and medullary degeneration the granular corpuscles contain globules colouring red or orange-red with Sudan, and pink or blue with Nile blue, but comparatively few of these are affected by neutral red; similar droplets exist free in the tissues. Doubly refractile material has the form of bright needles in the globules, in the cells or in the tissues and is most abundant in the centre of the damaged area where the granule cells are also most plentiful.

Similar results have been obtained by other workers in a variety of pathological processes.

From time to time various inclusions have been described which possess the property of staining metachromatically with toluidin blue. Most commonly met with in the peripheral nerves where they were first shown by Liebreich in 1865, they are also encountered in the central nervous system, particularly in association with degeneration of medullated nerve fibres. Reich [25] employed the term π-granules to designate these bodies which he supposed consisted of protagon. Protagon is not, however, a chemical entity but a mixture of phosphatides and cerebrosides. These granules are not soluble in alcohol, ether or xylol and hence appear in paraffin and celloidin sections. In the glial and endothelial cells they are associated with other inclusions, which colour with scharlach and which stain yellowish or greenish with toluidin blue. Alzheimer concluded that these last were derived from the basophil metachromatic granules. The same cells assume an intense red tint with neutral red, but it is difficult to state to which of their varied contents this reaction is to be attributed.

The π-granules are especially abundant in such morbid conditions as epilepsy, arterio-sclerosis, senile dementia and progressive chorea, being found chiefly in the white matter. Bonfiglio [3] found that they stained with osmic acid, but not with Weigert's myelin stain.

On summarizing the literature given above, it is seen that many observers have recognized the presence, in degenerative conditions, of such bodies as the neutral fats, fatty acids, cholesterin, cholesterin esters,

phosphatides and cerebrosides. But little attention has been paid to the period at which these various substances appear after the original pathological event, where that could be indicated with certainty. The staining reactions employed have been numerous; many more have been used than are referred to here, but no series of cases in which any of these have been used throughout for purposes of comparison is recorded.

The aims, therefore, of the first part of the paper are :—

(1) To determine the nature, mode of production and time relation of the various products of nervous disintegration.

(2) To compare the results obtained by various staining methods in a series of cases and so to ascertain the value of these methods.

Methods.

The brain and cord of each case was fixed whole, after removal, by suspension in 10 per cent. formol saline. The tissue to be examined for fatty substances was cut by the freezing microtome and stained by the following methods :—

(1) Scharlach R (alum hæmatoxylin being employed as counter-stain) :
   (*a*) On untreated sections.
   (*b*) After immersing sections for twenty-four hours in acetone, alcohol, chloroform or xylol.
   (*c*) After mordanting by Ciaccio's method [6] with subsequent immersion in alcohol, a mixture of equal parts of methyl alcohol and chloroform or a mixture of equal parts of acidified absolute alcohol and ether.

(2) Osmic acid before and after the action of potassium bichromate.

(3) The Nile blue method of Lorrain Smith [16].

(4) Klotz' method [14] for staining fatty acids.

(5) The Kultschitsky-Pal method for myelin. A modification which is described in an appendix was employed.

(6) Neutral red.

(7) Unstained sections were examined for coloured pigments and with polarized light for doubly-refracting lipoids.

Tissue was also passed through celloidin and the sections stained by general and special tissue stains.

Normal Myelin.

At this point it is convenient to review the staining reactions of the normal myelin. The results in the first four cases show that with alum hæmatoxylin and scharlach the colour assumed by the medullary

sheaths is a brick-red, which is a combination of a faint blue shade imparted by the former and a yellow-brown element given by the latter stain. This colour varies slightly with the hæmatoxylin used, older samples and those containing a low percentage of alum tending to render the colour more purple.

When the cases of amaurotic family idiocy are recorded, it will be shown that certain phosphatides and cerebrosides stain in this way with hæmatoxylin and scharlach and it may be these constituents of the myelin sheath that are responsible for this reaction.

With Nile blue the colour is a blue or purplish-blue and osmic acid is reduced before and not after chromication. By the Kultschitsky-Pal method, which is of course a modification of Weigert's original myelin stain, a deep blue colour develops after one or two days mordanting, but when mordanting is continued for four days the colour is less intense, while if the process is continued still further no staining takes place. An exception was seen in the fourth case where, after application of the mordant for five days, the colour was no less intense than on the first and second days. With the method of Lorrain Smith no coloration results.

When examined in polarized light, the myelin is seen to be brightly refractile, and if the nerve fibres are cut in transverse section the sheath appears as a circle with a dark centre from which radiate four dark streaks set at right angles one to another.

Acetone has but little effect on the staining properties with hæmatoxylin and scharlach but the double refraction is less marked after its use. Alcohol removes a considerable part, but even after three days a pale staining with hæmatoxylin and scharlach can be seen. Double refraction is often scarcely noticeable after the use of this solvent but its degree is somewhat variable. After chloroform only a pale yellowish-brown staining material is left which is not doubly refractile and is very scanty. It will be noted that this residue does not take on any tinge with the hæmatoxylin and that it was not present in Case III. Acid alcohol and ether complete the removal if any substance remains after chloroform. Thus the solubilities of the components of the medullary sheath correspond to those of cholesterin, phosphatides and cerebrosides, of which it is believed that myelin is composed.

Description of Cases.

The first three cases are of tract degenerations at different periods after the initial lesion.

Case I.

A boy, aged 13, suffered from ulcerative endocarditis. Six weeks before death he had cerebral embolism causing hemiplegia. The post-mortem examination was performed within twenty-four hours of death and the middle cervical segments were taken for investigation.

Degeneration was in progress in the affected, direct and crossed pyramidal tracts and was marked in hæmatoxylin and scharlach sections by globules of varying dimensions varying in tint up to a pale yellow-orange. Many of these were composite structures of concentric arrangement, colouring more or less intensely in different parts. Others were of the same hue as normal myelin but without the structure of the myelin sheath, and yet others while possessing its tubular structure were greatly enlarged. A certain number of perfectly normal fibres traversed the damaged area. The great bulk of the fatty debris was extracellular, and wandering cells had not yet commenced to transport it to the perivascular spaces.

A few brightly anisotropic crystals, which proved to be *cholesterin*, were present. Some of the colourless "globules" possessed a thin rim of doubly refractile material, but as their contents stained neither as fat nor by ordinary tissue stains (on frozen sections) they cannot have been other than fluid in nature. In other cases the centres consisted of cholesterin.

Most of the doubly refractile material showed the refraction effects of *myelin*, viz., a circle of refractile matter divided into four segments by a dark cross. Even the pale orange globules presented this appearance in many instances and evidently included a considerable quantity of unchanged myelin. The myelin globules and normal myelin tubes became grey-black with osmic acid before but not after chromication, stained purplish-blue with Nile blue, and in Kultschitsky-Pal sections assumed an intense blue colour after one day's mordanting. They still stained well but were less anisotropic after acetone; were much paler and almost isotropic after alcohol and were removed almost entirely by chloroform. But even after chloroform a scanty residue staining yellowish-brown with scharlach was present and required acid alcohol and ether for its removal.

Fatty acid was present in varying proportions in some of the globules as revealed by Klotz' method, and Ciaccio's method showed that a small proportion was in the form of saturated fatty acid. The globules blackened with osmic acid, but after chromication reduction occurred in only a limited number. With Nile blue a purplish-blue coloration was seen, and by the Kultschitsky-Pal method the best results were obtained after two and three days' mordanting. These globules were soluble in all reagents.

A part of the pale orange lipoid was insoluble in acetone but all was removed by alcohol. After chloroform a framework was left to some of the globules which did not stain with scharlach and was soluble in acid alcohol and ether.

A few of the anterior horn cells contained *lipochrome pigment* staining orange with scharlach, dark brown with osmic acid even after chromication,

orange-red with neutral red, blue with Nile blue and blue-grey with Kultschitsky-Pal after three to five days' mordanting. In toluidin blue preparations they were hidden by the large and numerous Nissl bodies. They were insoluble in all the solvents employed and were not doubly refractile. In unstained sections this lipoid was faintly yellow in tint.

Case II (figs. 1 and 2).

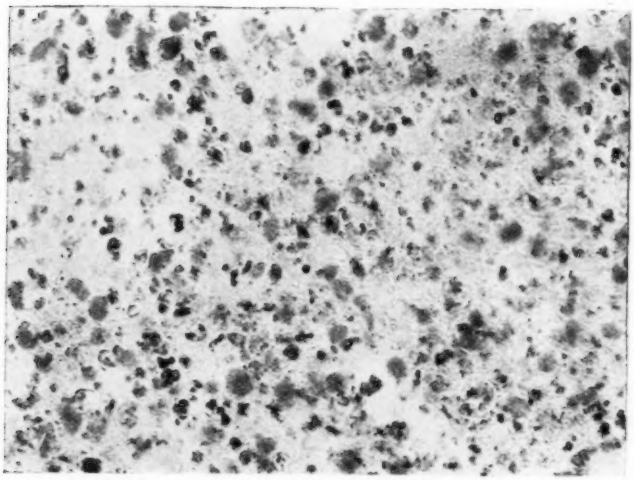
Female, aged 45. Paraplegia had commenced five months, and had become absolute three months, before death, which was from sepsis. The post-mortem examination, which was held within twelve hours of death, revealed a gummatous condition of the dura in the lower dorsal region, which involved the cord on the right side. The part of the cord not visibly infiltrated was much shrunken at this level and ascending and descending degenerations were in progress above and below the lesion respectively. The lower cervical region was examined.

FIG. 1.—A section of the spinal cord of Case II stained by the Kultschitsky-Pal method to show the degenerated tracts.

With hæmatoxylin and scharlach the degenerated areas were seen to contain numerous masses and globules of fatty nature mainly extracellular in position. Large bright orange-red globules and crystalline masses consisted of *neutral fat* and *cholesterin*: both of these substances occurred separately. The former blackened with osmic acid before and after chromication, stained pink with Nile blue and reached a maximum coloration with Kultschitsky-Pal on the fourth day. The latter was doubly refractile. The contents of granular corpuscles away from the degenerated areas contained more neutral fat and but little cholesterin. These substances were soluble in all reagents.

Unsaturated *fatty acids* were present in small amount and were removed by all solvents. No saturated fatty acid could be demonstrated.

Some normal *myelin* sheaths traversed the degenerated area and some of the globules gave the reaction of this substance and probably consisted of myelin as yet unchanged chemically. They stained brick-red with scharlach, black with osmic acid before, but not after, potassium bichromate, and purplish with Nile blue, and they showed the characteristic appearances in polarized



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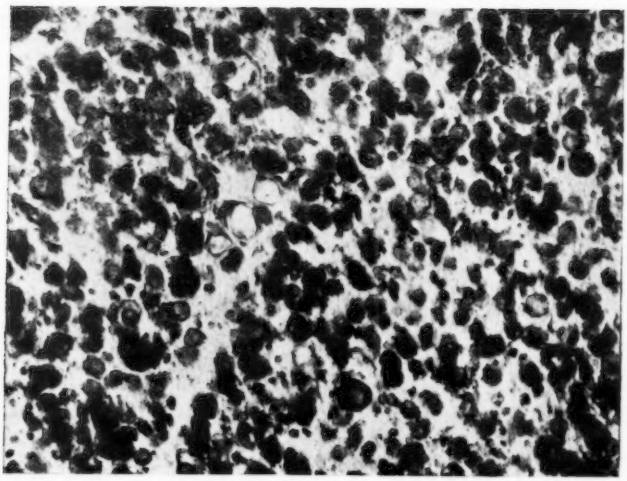


B

FIG. 2.—A and B, High-power views of the degenerated areas in Case II after one and four days' mordanting by the Kultschitsky-Pal method. The increased intensity of staining with prolonged mordanting is well seen.

light. They were unaffected by acetone, partially dissolved by, and less refractile after, alcohol, while chloroform left an isotropic debris staining a faint brown with scharlach and soluble only in acid alcohol and ether. By the Kultschitsky-Pal method the best staining was on the first and second days.

Some of the extracellular lipoid stained less intensely with scharlach and a part of this resisted solution in acetone but was removed by the other solvents employed. Such material was anisotropic to a limited extent.

Many of the cells of the anterior horns, Clarke's column and the posterior horns showed collections of *lipochrome* pigment. Where this was scanty the granules lay between the Nissl bodies, but in most cases they were clumped together near one pole of the cell, while a few cells contained little else than pigment granules. The vessels, the ependymal cells of the central canal and the neuroglial cells contained similar granules. Their properties have already been enumerated but it must be mentioned that in sections stained by toluidin blue a distinct fine blue network was in a few instances visible between the individual granulations.

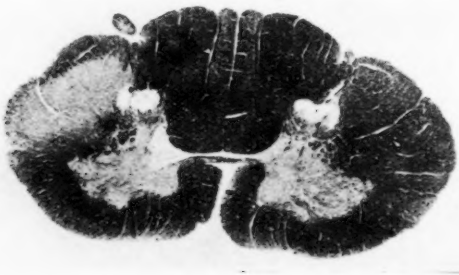
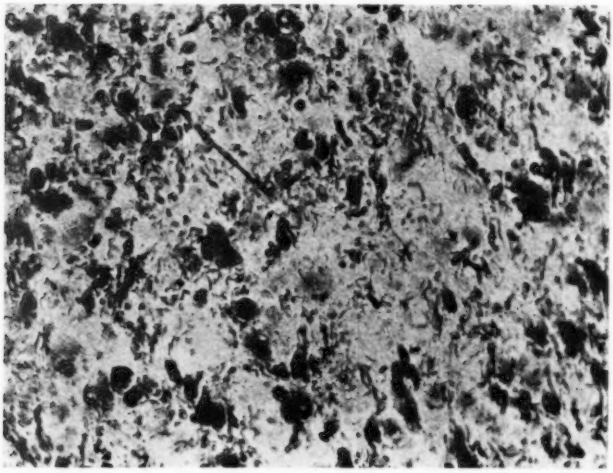


FIG. 3.—A section of the spinal cord from Case III, stained by the Kultschitsky-Pal method to show the degeneration of the pyramidal tract.

Case III (figs. 3 and 4).

A male, aged 62, suffered from a hemiplegia of vascular origin during the last six months of his life. The post-mortem examination took place twenty-four hours after his death from uræmia. Sections were taken from the upper cervical region and a well marked advanced degeneration of the direct and crossed pyramidal tracts was observed.

Much of the fatty material lay in large phagocytic cells and consisted of finer and coarser granules and globules and definitely crystalline masses. These contained *neutral fat* and *cholesterin* in varying proportions. The contents of migrating granular corpuscles were chiefly neutral fat. Of the extracellular lipoids these bodies formed a large part. By the Kultschitsky-Pal method the neutral fat stained most intensely on the fourth day.



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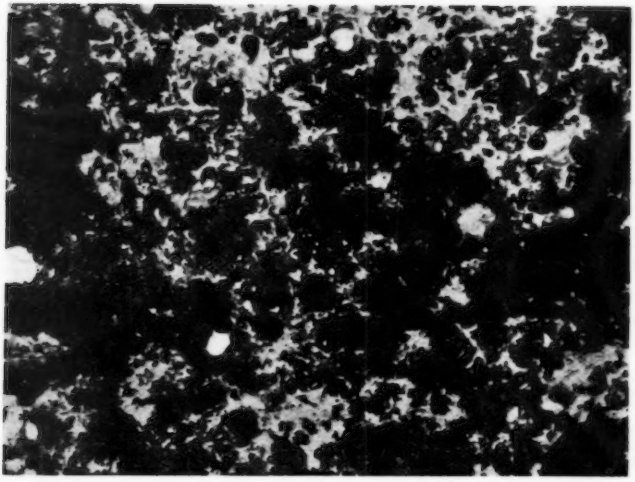

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FIG. 4.—A and B, high-power views of the degenerated tract in Case III, stained by the Kultchitsky-Pal method. The sections were mordanted for one and four days respectively.

Unsaturated fatty acid was present in small amount as shown by Klotz' method.

A certain number of normal myelin sheaths were seen in the degenerated area and gave the reactions already described except that they were completely soluble in chloroform.

All the products of degeneration were removed by acetone, alcohol, &c.

The cells of the grey matter showed changes in keeping with the age of the patient. A few were normal, several in each section were mere bags of lipochrome pigment with but little normal protoplasm; the majority contained a moderate amount of lipoid collected near one pole of the cell. Here again in toluidin blue sections the golden green granules were seen to be separated by a fine blue network with slight swellings at the nodal points. Though in some cases a similar appearance might have been due to the refractility of the granules, in one section stained with hæmatoxylin and eosin there was no doubt concerning the reality of the intergranular network in at least one cell.

Similar granules were encountered in the walls of some of the vessels, in the large astrocytes of the affected pyramidal tract and in the ependymal cells lining the central canal.

π-granules were seen in the anterior and posterior nerve roots for the most part grouped around the nuclei of the neurolemmal sheath, but a number were apparently lying free between the fibres. The presence of these granules in paraffin sections showed that they were insoluble in xylol.

Discussion.

There is no reason to suppose that the process of ascending degeneration differs in any way from that of descending degeneration and these three cases may be taken, therefore, as presenting the same process at different stages. The sections examined were in each case from the same region of the cord, viz., the cervical region.

In Case I, the lesion causing hemiplegia was of sudden onset and occurred six weeks before death. A number of normal fibres traversing the affected pyramidal tract represented those which at a higher level had escaped destruction. A second group, while showing the same tubular structure as the preceding, were greatly swollen and the question arises as to the cause of such swelling. After the lapse of six weeks it might be expected that a fibre which had been irreparably damaged in some part of its course would exhibit more pronounced changes; such certainly obtains in Wallerian degeneration of the peripheral nerves. On the other hand it is known that around an embolic focus in the brain considerable œdema occurs which interferes with the nutrition and function of the nervous elements, but not to an extent which prevents their recovery on its subsidence; indeed, partial recovery

from a hemiplegia often takes place so rapidly during the first few weeks after the ictus, that many of the fibres originally involved cannot have sustained more than a temporary injury. The presence of these swollen medullary sheaths may possibly be explained in this manner. Had the appearance been due to an artefact it would scarcely have been confined to one pyramidal tract as was the case.

Many of the globules in the degenerated area consisted of unchanged myelin, possessing the characteristic staining properties and refraction effects of that substance, while others though colouring orange with scharlach had the same appearance when examined by polarized light and evidently included a considerable amount of myelin. Globules containing fatty acids in smaller or greater proportions were revealed by Klotz' method and some of these were seen, by Ciaccio's method, to belong to the saturated series. The highly anistropic centres of some of the globules did not stain by any method but were readily soluble in all solvents; these could only have been cholesterin in a pure condition. The material colouring orange with scharlach was probably a mixture of neutral fat, fatty acid, phosphatides and cerebrosides. The first two constituents were responsible for the purplish tint with Nile blue and were soluble in acetone; the feeble reduction of osmic acid after chromication suggested that their amount was not large. The third remained after the action of acetone but was removed by other solvents, while the cerebrosides formed the colourless framework of the globules which was seen after the application of chloroform and was removed by acidified alcohol and ether. It will be noted that if this supposition is correct the phosphatides present, though conforming to the solubilities of this group of compounds, were atypical inasmuch as they stained with scharlach and that the cerebrosides did not dissolve in chloroform. These points will be discussed later as will the results obtained by the Kultschitsky-Pal method.

The products of degeneration were chiefly extracellular and migration of granular corpuscles towards the perivascular spaces had not commenced.

In Case II, the lesion was not of abrupt onset, but was steadily progressive over a period of two months. Conduction in the cord had been completely interrupted three months before death and the tract degeneration was consequently of between three and five months' duration.

In the degenerating area very few of the globules, droplets and masses consisted of one lipoid substance in a pure condition, but were rather mixtures of several such bodies. This renders short description

very difficult. Colourless doubly refractile crystals, soluble in acetone, were undoubtedly composed of cholesterin and much cholesterin was also present in the masses colouring with scharlach, causing them to assume a semi-crystalline appearance and to be doubly refractile. Fatty acid was present in some of the globules, as shown by Klotz' method, but the existence of saturated fatty acids could not be demonstrated. The bulk of the lipoid was in the form of neutral fat, hence the brilliant staining of much of the material with scharlach. Removal of the majority of the lipoids by acetone left a small amount of pinkish, doubly refractile substance, probably cholesterin esters, and a few brownish rings which may have been phosphatides and which formed the colourless rims of some of the globules staining pink with Nile blue. Both of these were absent in sections treated with alcohol. Finally, a few globules of unchanged myelin and a few normal myelin sheaths were encountered.

A greater proportion of the products of degeneration were intracellular than in the first case but the majority was still free in the tissues. Those in the former situation assumed a deeper tint with scharlach and consisted almost entirely of neutral fat and cholesterin. Granular corpuscles had made their appearance and were engaged in the transportation of the fatty debris to the Virchow-Robin spaces, being found at some distance from the affected tracts; their inclusions were composed chiefly of neutral fat with but little cholesterin.

Case III illustrates the changes found in tract degeneration at the end of six months from a single non-progressive lesion.

Pure cholesterin crystals, neutral fat and mixtures of these substances were abundant but fatty acid was demonstrable in small quantities only. Saturated fatty acids were not detected and the other lipoids met with in the preceding cases were absent. A number of normal myelin sheaths indicated the incomplete nature of the destructive process.

Much of the fatty material had been engulfed by phagocytic cells and was largely in the form of neutral fat, while a still greater preponderance of neutral fat was observed in the granular corpuscles which had reached the Virchow-Robin spaces at some distance from the seat of degeneration. The granules in the anterior and posterior roots could not, from their bilateral distribution, have been directly connected with the hemiplegia and their presence may, perhaps, be explained as an effect of the uræmia from which the patient suffered.

It is at once obvious from the foregoing that the time factor has an enormous influence on the nature of lipoids present in an area of secon-

dary degeneration resulting from a single, stationary, destructive lesion and that no account of such a degeneration can be considered complete unless this factor receives sufficient attention. Whether, at a given period after the onset of myelin disintegration, the fatty products are always the same or whether the process may be accelerated or retarded by the constitutional condition of the subject, is a point requiring more extended observation, but of which the practical importance is readily apparent. It is possible, however, to indicate the alterations occurring in the myelin sheath from its fragmentation to its conversion into various end products.

Myelin is a complex body containing phosphatides, cerebrosides and cholesterin, together with a small percentage of sulphur in lipoid combination, the last being unrecognizable by any known histological method. Having become resolved into globules and droplets the myelin appears to separate into its individual constituents. Cholesterin is seen alike in early and in late stages, being present at the sixth week and again and in larger amount at the end of three and six months. Some, apparently, is combined with fatty acid to form cholesterin esters, but these were detected only in Case II and then in small quantity, so that they must either be removed with great rapidity or synthesized in negligible amounts. The granular corpuscles at first contain cholesterin but as they approach the perivascular spaces it disappears leaving neutral fat as the sole constituent of these elements. The mechanism of its removal is not clear but it normally exists in solution in the blood and may be absorbed directly by the tissue fluids.

Phosphatides and cerebrosides are found in smaller amount and had disappeared in Case III after six months. It would seem that they are rapidly broken down and since their molecules always contain a fatty acid radicle it must be supposed that they contribute in part at least to the fatty acid seen at the sixth week and third month.

In agreement with this supposition is the observation that at the end of six months, when phosphatides and cerebrosides were no longer found, fatty acid was present in minute amounts only. The fatty acid radicle varies in the different members of these groups and both saturated and unsaturated acids may be derived from their splitting. In Case I both types were present, for the residue by Ciaccio's method did not represent more than a small part of the fatty acid coloured by Klotz' stain. Probably the saturated series disappears first, for in Cases II and III none was found and it is to be expected that being in relatively small amount it is more readily dealt with.

Neutral fat is the ultimate product of myelin degeneration, and after six months the majority of the lipoid is in this form. It has already been shown that in the granular corpuscles in the vicinity of the Virchow-Robin spaces, where the most advanced changes are to be sought, neutral fat was the predominant or even the only inclusion. Lecithin may be regarded as a neutral fat in which one of the fatty acid radicles is substituted by phosphoric acid combined with choline, and although it is not known how this body breaks down it is possible that by removal of the substituted group and its replacement by glycerol neutral fat may be produced. Again, since fatty acids are liberated in the manner detailed above it only requires glycerol to convert them into neutral fat. This may be to some extent supplied from the glycero-phosphoric acid of the phosphatides, and it is recognized that glycerol may be derived from hexoses (e.g., dextrose), the molecules of which split into two molecules of glycerol aldehyde, a body capable of being transformed into glycerol on reduction.

A discussion of the types of cells engaged in these chemical reactions and in the removal of the end products is not within the scope of this thesis. But as Jakob has shown [11, 12], the various processes of lipoid alteration are conducted by relays of myeloclasts and myelophages which engulf the lipoid substances, alter their constitution and then degenerate and deposit their contents in the tissues to await the advent of their successors which continue the breaking down and at a later stage remove the debris to the channels of elimination.

A discussion of the other features of these cases is reserved until a later stage.

Disseminated Sclerosis.

The next case illustrates the disintegration of myelin from an entirely different cause. In disseminated sclerosis the attack is directed upon the medullary sheath which is stripped off the axis cylinder leaving the latter bare, but, as a rule, uninterrupted in its continuity. Even though it may be shown that the chemistry of the process is similar to, or identical with, that in the preceding case, it would manifestly be wrong to class the results of a primary local toxic onslaught on the myelin with those of a trophic disturbance from a mechanical lesion at a distance. The duration of the degeneration also can only be problematical, for not only is the period over which the noxious substance continued its action uncertain, but in a disease where the lesions are multiple and scattered throughout the nervous system the symptoms due to each

are indeterminable, and in judging the age of a focus it is necessary to depend on appearances which themselves vary within certain limits, in other words on the condition of the neuroglia.

Case IV.

A male, aged 29, had suffered from the symptoms of disseminated sclerosis for four years. The post-mortem examination was held within twenty-four hours of death. A fairly recent patch in the centrum semi-ovale of one cerebral hemisphere was taken, the age of which, judging by the character and degree of the neuroglial overgrowth, was some six to nine months.

At one end of the focus, where demyelination was complete, most of the fatty material had been removed from the tissues and was arranged in the form of thick cuffs around the vessels; elsewhere in addition to deposits in the Virchow-Robin spaces there were numerous masses scattered throughout the tissues. At the periphery of the patch was a narrow zone in which some myelin still persisted, and here the products of degeneration were especially plentiful. Proceeding outward still further from the centre of the plaque the nerve fibres rapidly became normal in appearance, and only an occasional granular corpuscle with its contents was seen between them, though the perivascular spaces for some distance out were still filled with these phagocytic elements.

The disintegration products were both intracellular and extracellular in position. The lipoids present consisted chiefly of larger and smaller globules of neutral fat, highly refractile crystals of cholesterin and mixtures of these bodies. In the Virchow-Robin spaces of the cortex at a considerable distance from the patch granular corpuscles containing neutral fat were encountered. By the Kultschitsky-Pal method the neutral fat stained most darkly after five days' mordanting.

A certain proportion of the granules in the vessel walls and astrocytes gave the reactions of lipochrome pigment, as did the nerve cells of the adjacent cortex. No fatty acid was detected in sections stained by Klotz' method. A few π-granules were revealed by the action of toluidin blue, and these were insoluble in alcohol and in xylol.

After the application of acetone there was left in the granular corpuscles a very finely granular residuum which stained orange-brown with scharlach, was not doubly refractile and while partially soluble in alcohol and in ether and almost entirely in chloroform and a mixture of methyl alcohol and chloroform, required xylol or acid alcohol and ether for its complete removal.

The normal myelin possessed the usual properties except that by the Kultschitsky-Pal method, after five days' mordanting, it still coloured an intense blue, whereas in the preceding cases the deep colour seen in the earlier stages had faded considerably at this period. At the margin of the focus the myelin sheaths presented numerous varicosities.

Discussion.

In this case the myelin sheaths had been completely destroyed except at the margin of the focus, where a certain number survived in a damaged condition. These, when traced outwards, rapidly became normal. *Neutral fat* and *cholesterin* represented the majority of the lipoid present, and mixtures of these substances occurred in all proportions, but after the various fat solvents some scharlach-staining material remained, possessing, more or less, the solubilities of the phosphatides and cerebrosides. Fatty acid was not recognized. A few lipochrome granules were met with in the vicinity of the vessels and in the glial cells. In the oldest part of the patch, removal of the debris had reached such a stage that a very little was left in the tissues, the majority having been transported to the perivascular spaces: but nearer the edge where, presumably, the process had continued to spread for some weeks or months, the scavenging had been less complete and much lipoid still awaited removal.

In the Virchow-Robin spaces of the cortex neutral fat existed in small amount. This was not more abundant in the regions nearest to the patch, which was at some distance from the surface, nor was there a continuous and increasing occupation of these spaces by the fat as the focus was approached, such as would suggest an origin from the diseased area. It is probable that it may have been derived from a degeneration of the cortical elements, for these exhibited large quantities of lipochrome pigment and were obviously not normal.

Lipochrome Pigment.

The lipochrome pigment must now be described.

The lipochrome pigment occurred in largest amount in the nerve cells, but was also found in glial elements, in the cells of the vessel walls, particularly in their endothelium, and in the ependymal cells lining the central canal of the spinal cord. In advanced life its presence in moderate amount may be regarded as almost normal, but at an earlier age it is found in conditions in which a toxæmia is present for a considerable time before death. Thus in Case I, which was one of ulcerative endocarditis, its formation had already begun at the age of 13, while in Case IV considerable collections were present in the cortical neurons, the patient having suffered from disseminated sclerosis for four years before his death at the age of 29.

When in small amount in the nerve cells, the granules of pigment

lay among the Nissl bodies, but when more numerous they tended to form a cluster towards one pole of the neuron, and in extreme cases almost entirely filled the body of the cell. In a given case, all the nerve cells were not equally involved, some being almost or quite free from lipoid, others containing a moderate quantity, and still others being reduced to mere bags of pigment granules. Occasionally a definite protoplasmic network was seen separating the individual granules which were enclosed in its meshes. In the glial cells the granules were not numerous and were scattered in the protoplasm, while in the ependymal cells they were grouped around the nuclei. In unstained preparations the lipoid was seen to possess a pale yellow colour and was not doubly refractile. With scharlach the colour assumed varied somewhat with the sample of dye employed but was usually a bright orange-red. Sometimes, however, a paler yellow-orange tint was seen, especially when the granules were small, suggesting that the colour depends partly on the thickness of the layer of lipoid through which the light passes on its way to the eye. The granules become golden-green with toluidin blue, orange-red with neutral red, deep blue with Nile blue, and they darkened with osmic acid both before and after chromication. With the Kultschitsky-Pal method they stained feebly or not at all after one day's mordanting, but with longer mordanting a deep grey, blue-grey, or blue-black colour developed which reached a maximum in from three to five days, and thereafter commenced to fade. The pigment resisted solution in all solvents and its staining reactions were unaffected by any of these. Even hot xylol and acid alcohol and ether did not effect its removal.

From this account it is obvious that the lipochrome pigment possesses highly characteristic properties, viz., that it stains readily with all the lipoid staining reagents and at the same time is extremely resistant to their solvents. It is not only to the histologist that the solution of this lipoid is a problem; apparently the cells have the same difficulty of disposing of it, for in cases where the neurons disappear, either from degenerative influences in the living tissue or from autolysis consequent upon faulty or late fixation after death, the site of the cell is marked by a collection of lipochrome granules which are quite unchanged in their appearance and staining reactions.

The insolubility of the granules has given rise to considerable difficulty in explaining their nature. Marinesco's supposition [37] that combination with protein has occurred is unlikely, for, as will be shown later, such combination prevents the reaction with scharlach. More-

over, the series of intermediate bodies between the lipoid in amaurotic family idiocy which, as I shall show, consists of phosphatides and cerebrosides, and the lipochrome pigment, suggests that the latter is of similar nature. Whether it is actually a phosphatide or cerebroside, or whether some chemical change has taken place during its formation, giving rise to a closely allied substance, cannot definitely be decided from the facts available.

(B) Amaurotic Family Idiocy.

Literature.

In amaurotic family idiocy and the allied condition of cerebro-macular degeneration the nerve cells undergo very characteristic degenerative changes. The cell body becomes enormously distended, the dendrites and very occasionally the axons are also irregularly swollen and lipoid granules of a peculiar nature make their appearance. The reports of various observers on the properties of these granules vary considerably, depending, no doubt, on the period of the disease at which the patient has succumbed.

In Spielmeyer's case of the juvenile type [33] the lipoid stained golden yellow by Nissl's method and yellow-green with iron alum hæmatoxylin. It was insoluble in ether, xylol, &c., and stained feebly with scharlach R, both before and after the use of these solvents. After chloroform it was coloured blue with Nissl's methylene blue. Osmic acid and Weigert-Pal gave negative results.

Vogt [34] in a case of the infantile type found that the granules stained with Weigert-Pal and iron alum hæmatoxylin but not with fat stains. In two cases of the juvenile form the granules stained with iron alum hæmatoxylin but not with Sudan III or with other dyes.

Carlyll and Mott [5] record a deficiency of organic phosphorus and sulphur with an increase of water-soluble extractives containing those elements in brains of children dying of amaurotic family idiocy, so that it cannot be supposed that there is an increase in the total amount of lipoid bodies. Mott believes that the nucleus provides a splitting ferment but not a synthetic enzyme, and thus lipoid separated from the complex cytoplasmic molecules accumulates in the cells. In the later stages the appearances suggest its conversion into an emulsion. The granules in both the nerve-cells and granular corpuscles stain with scharlach R, and in the former situation are probably composed of a protoplasmic substance covered with a fine film of fat or soap. They are soluble in alcohol and ether.

Alzheimer [1] succeeded in dissolving most of the granules by the application of alcohol for one hour at 50° C. They did not stain with scharlach or with osmic acid after chromication but were coloured by Ehrlich's hæmatoxylin.

Schob [32] in cerebro-macular degeneration describes granules assuming a golden green tint with Nissl's method, a red colour with eosin and with scharlach and appearing grey-black or black with iron hæmatoxylin. They were insoluble in alcohol and Marchi's method gave negative results.

Hume [10] in the infantile form found that the lipoid in both nervous and glial elements stained with scharlach.

Dide, Guiraud and Michel [8] in the juvenile type showed that the granules in the nerve-cells were coloured blue wiih Nile blue and yellow-red by Sudan III. Many of the glial cells contained red granules. The substance was insoluble in alcohol and chloroform, did not react like fatty acid by Fischer's method, was Gram-positive, became brown with osmic acid and in part blue-black with iron alum hæmatoxylin. They considered that it was of the nature of phosphatides and cerebrosides and bore no analogy to the normal lipochrome pigment. In all probability it was derived from a complex lipoprotein but they were uncertain whether that in the glial cells was derived from the neurons or was a manifestation of a primary degeneration in these cells.

Schaffer [28, 29, 30, 31], who has made numerous contributions to the subject, states that there is a primary swelling of the cell, due to the absorption of fluid from the ambient medium, leading to opening, out of the cyto-reticulum, the meshes of which are at first empty but soon contain fuchsinophil granules and later granules staining blue with the Weigert-Pal method. As the disease progresses these reactions are lost, the network becomes indistinct and the cell assumes a uniform reddish colour with scharlach R, without showing definite fatty granulations. This he terms the prelipoid phase. He points out the close resemblance of these products to lecithin and justifies the use of the expression "lecithinoid degeneration." The infantile cases usually prove fatal at this stage, but in cerebro-macular degeneration a further conversion of the prelipoid substance causes scharlach-staining granules to appear, while in the family idiocy without blindness of Erwachsen a still more advanced, osmio-reductive phase is reached. He regards the process as being similar to that producing the senile lipochrome pigment.

The phagocytic cells contain scharlach-staining granules or dull red substance, according to their situation, the former being found nearer the vessels. Those engaged in neuronophagy may even show a substance with an affinity for hæmatoxylin. The fibrillar neuroglia, on the other hand, undergoes a degeneration analogous to that in the nerve cells.

Marinesco [21] has made the important observation that in this disease there is a diminution in the amount of oxydases in the nerve cells, the amount of these varying inversely with the quantity of lipoid present. In his case many of the cells stained diffusely with Sudan III, but some possessed fine Sudanophil granules while the perivascular cells had orange-red granules. Much of the lipoid stained by the methods of Ciaccio and Dietrich and still more with iron alum hæmatoxylin. The myelin had undergone considerable rarefaction. He regards the disease as an expression of altered activity of the cellular ferment.

Thus it appears that no conformity of opinion has been reached, either as regards the exact nature of the products of degeneration in these conditions or as to their origin. This investigation was conducted with the object of determining their origin and nature, and if possible of correlating the process with other degenerative processes in the neuron.

Case V (figs. 5 and 6).

This was a case of amaurotic family idiocy in a Jewish baby. No clinical notes were at hand and only one cerebral hemisphere was available for examination.

In sections stained by toluidin blue the changes seen in the nerve cells were widespread, and in all ways typical of the condition. The cell body consisted of a delicate reticulum with slight swellings at the points of intersection of the network, enclosing a pale pink, metachromatically staining substance which had for the most part resisted solution in the alcohol and xylol—though towards one extremity of the pyriform elements or at the periphery of the globular cells, the whole of the contents of the meshwork had disappeared. In many instances only the nodal points were visible and the cell had a finely-stippled appearance; on the other hand, in some, chiefly the smaller, elements the intersecting bands were relatively coarse and the meshes large.

In the large cells of the striatum (caudate nucleus and putamen of the lenticular nucleus) the peripheral portion of the cells was often completely devoid of either network or metachromatic substance, appearing merely as an empty space, while those of the globus pallidus showed only the faintest stippling at the end remote from the nucleus.

With hæmatoxylin and scharlach it was obvious that the meshes of the

network were occupied by granular matter, mainly of a rosy red colour somewhat similar to that of the myelin in sections which have been overstained with scharlach, but appearing in those where the reticulum was less distinct of a paler and more yellowish red. Thus while the cortical cells and those of the claustrum and optic thalamus were of the former hue, the large cells of the basal ganglia showed a considerable amount of paler substance in the part of the cell remote from the nucleus, and the small elements of the striatum also assumed a yellowish tint.

The lipoid was doubly refractile, but not to a high degree, and in the small cells of the striatum not at all. Acetone removed from the granules some constituent of a yellow colour, for after its application their colour was

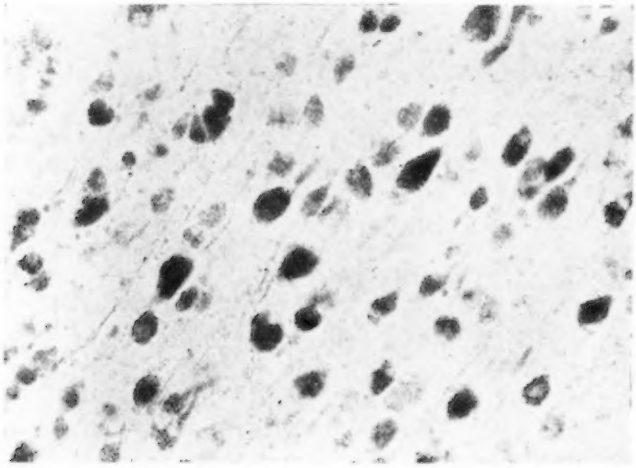

FIG. 5.—A section from the cortex of Case V, stained by the Kultschitsky-Pal method. The duration of mordanting was four days and at this period the lipoid granules in the nerve-cells assumed, in many cases, a deep coloration.

a more purplish red; they were no longer anisotropic, but no diminution in their bulk was evident. Alcohol dissolved the greater part and chloroform (also methyl alcohol and chloroform) somewhat more, but a small residue resisted the action of all solvents except acid alcohol and ether.

No fatty acid could be demonstrated, with osmic acid no reduction took place, and no fuchsinophil granules were present. With Nile blue a deep blue colour was seen. With the Kultschitsky-Pal method, on the first day most of the cells were seen to contain very pale bluish-grey granules, but of the small cells of the striatum only a minority gave this reaction. After two days the large cells of the striatum and the cells of the cortex, globus pallidus, optic thalamus and claustrum, showed darkly staining granules, but, although

more of the small cells of the striatum stained than on the first day, their coloration was feeble when contrasted with that of the large cells. In most situations a few cells remained untinted. Another forty-eight hours caused the large cells to become a more intense blue than the myelin, which was now fading, with the exception again of the small cells of the striatum, which were no darker than before. By the sixth day all elements had begun to fade.

Although certain tracts and bundles of fibres were more affected than others, in few regions did the myelin content of the white matter approximate to normal. The sheaths presented frequent small bulbous swellings along their course which imparted to them an extremely irregular outline. Many minute droplets, probably of the nature of fatty acids, were seen between the fibres, which, while not staining red or yellow with scharlach, gave an intense black colour with osmic acid before and after chromication, stained more darkly than the myelin in Kultschitsky-Pal preparations at all stages, coloured blue with Nile blue, and were not decolorized by Klotz' method. They were not doubly refractile.

Satellitosis was common, and with hæmatoxylin and scharlach the inclusions of the neuroglial cells showed all the stages in the transformation of the nerve-cell lipoid into neutral fat. The contents of the satellites could often not be distinguished by their reactions from those of the neurons they surrounded; but in others the colour was more yellow, whereas in many of the mobile elements they were stained diffusely a pale orange. A further development was the appearance in the wandering cells of exceedingly fine granules of an orange-red colour—at first isolated, but later more numerous, and eventually filling the whole of the cytoplasm, and of bright, doubly refractile crystals. The former gave the reactions of neutral fat, being stained pink with Nile blue and black with osmic acid even after chromication. They were soluble in acetone, &c., and by the Kultschitsky-Pal method assumed a pale violet tinge on the third day of mordanting, which had deepened considerably by the fifth day. The crystals gave the reactions of cholesterin. Such inclusions as have just been described were met with in granular corpuscles in the immediate vicinity of the vessels, and especially in the perivascular spaces. The vessels of both grey and white matter were surrounded by veritable cuffs of these cells. In all cases the fat was intracellular, except in the internal capsule, where some collections lay apparently free between the fibres; this appearance was probably due to the cutting, in transverse section, of one extremity of an elongated cell lying parallel to the direction of the fibre bundles.

After the neutral fat and cholesterin crystals had been removed by acetone, there was left in the cells, which had previously seemed full of such substances, a diffusely staining pale orange substratum in all respects similar to that which preceded their formation except that it was isotropic. It seemed that the doubly refractile element had separated out in the form of cholesterin, which had been removed by acetone. This pale orange residue was partly soluble in alcohol, in chloroform, and in a mixture of methyl alcohol and chloroform, and completely so in acid alcohol and ether.

Case VI.

This was also a case of amaurotic family idiocy. The child of Jewish parents, she had been normal during the first few months of life. At the age of seven months however it was noticed that she was becoming weak and losing the power of sitting up. Blindness developed, she lost all interest in her surroundings and died when sixteen months old. The cerebral hemispheres alone were examined.

In toluidin blue preparations the nerve cells were universally pale and swollen, being in many instances marked off from their surroundings by a thin blue rim. In some cases there was a pale blue network throughout the cytoplasm, but in a large number this was not stained, the protoplasm then

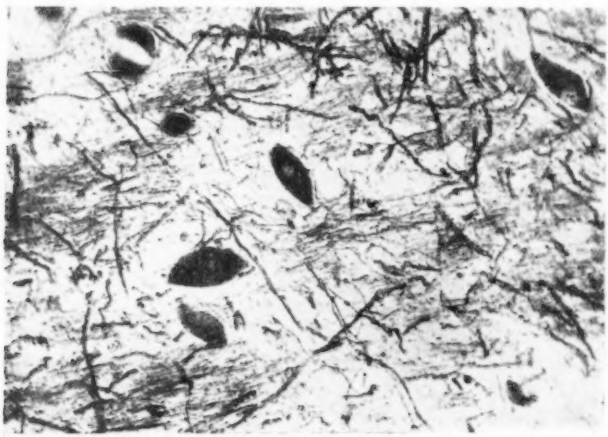

FIG. 6.—A section from the globus pallidus of Case V, stained in the same manner as the preceding. The lipoid is even more deeply coloured.

having a faintly stippled appearance. Yet others, especially in the globus pallidus, showed a darker network throughout. Some of the smaller neurons presented a deeply staining reticulum with wider intersecting bands and smaller spaces, while a few of the smaller elements in the putamen and caudate nucleus possessed a diffusely stained protoplasm with obvious reticulation.

With hæmatoxylin and scharlach the lipoid content of the cells was of a more purplish colour than in Case V and had a somewhat woolly appearance in places due to its uneven distribution within the cell. The intensity of staining varied according to the region examined, thus the cells of the claustrum were markedly paler than those of the cortex and certain groups of elements in the optic thalamus were darker than others. Generally speaking, however, the large cells were most deeply coloured. On the other hand some of the small

cells of the cortex were of a weaker and more yellowish red, while those of the striatum were almost all pale yellow in tint without any admixture of red.

The purplish substance was feebly anisotropic and remained so after acetone but not after alcohol. It was not visibly affected by acetone, but was almost entirely dissolved by alcohol, chloroform completing the removal. Ciaccio's method for fatty acid yielded no results; it stained blue with Nile blue but was left uncoloured by the methods of Klotz and with osmic acid. With Kultschitsky-Pal the distribution of the staining corresponded to that with ordinary hæmatoxylin and from a pale grey on the first day increased on the second and third to a medium blue-grey, fading considerably by the sixth day. Fuchsinophil granules could not be demonstrated.

The yellow contents of the small cells did not completely dissolve in any of the solvents, though alcohol and chloroform each caused some diminution in their staining power. They stained very poorly or not at all with Kultschitsky-Pal, even with prolonged mordanting, and assumed a blue tint with Nile blue, all the other reactions being negative. They were not doubly refractile.

The white matter was in all regions very deficient in myelin, its absence being much more conspicuous than in the preceding case. Otherwise the appearances in the two were very similar, e.g., irregular staining of the fibres, minute bulbous swellings in their course and minute globules of fatty acid lying between them.

As regards the neuroglia, satellitosis was very common. The majority of the phagocytes had purplish red contents which when treated with hæmatoxylin and scharlach behaved in a similar manner to that in the nerve-cells and were very rarely bright yellow in colour or studded with orange-red granules of neutral fat. A few such were met with, however, singly in the cortex, and in groups of three to five or six in parts of the optic thalamus. When they possessed orange-red granules these were of uniformly fine dimensions.

The vascular lymph spaces were filled with large granular corpuscles containing bright orange-red granules and droplets of neutral fat. In all the cortical areas the fat appeared almost exclusively in the form of small granules and was not so abundant as in the white matter and central grey masses. In the basal nuclei the tendency for larger granules and medium-sized globules to appear was noticeable and most of the lipoid was in this form. A fair proportion lay free in the Virchow-Robin spaces and the vascular endothelium exhibited a considerable amount in some regions. Its reactions were typical. By the Kultschitsky-Pal stain it coloured feebly on the second day and more intensely on the third, fourth and six days. A few of the granule cells in the perivascular spaces contained crystals of cholesterin. The neutral fat and cholesterin were removed by acetone, leaving an orange-yellow substratum, not in granular form, which caused them to resemble closely the occasional granular corpuscles of the grey matter which showed the same coloured substance prior to the development of orange-red granules. It was unaffected by alcohol, slightly decreased in amount after chloroform and almost totally extracted by acid alcohol and ether.

Case VII.

By the courtesy of Dr. Gordon Holmes and Dr. Greenfield the writer was permitted to study the lipoids present in the brain of a case of cerebro-macular degeneration which died at the age of 15.[1]

According to the region examined the neurons contained a varying amount of perfectly normal protoplasm separated sharply from the remaining area. This presented, in Nissl sections, a purplish blue network. In tissue which had been imbedded in celloidin the contents of the meshwork had been dissolved by the long immersion in alcohol and ether, but in frozen sections stained by the Nissl method granules of lipoid of a light or dark green colour were present.

With hæmatoxylin and scharlach different results were obtained according to the specimen of scharlach employed. Thus while with Grübler's scharlach the lipoid assumed only a very pale yellow tint, with Gurr's scharlach the colour varied from a pale yellow to a deep orange. In the *substantia nigra* the colour was more brown but the melanin usually found here was very scanty and these cells contrasted sharply with those of the *substantia ferruginea* which contained a normal amount of melanin. The lipoid substance was chiefly in the form of granules resembling the lipochrome granules of the senile nerve cell, but in some elements, especially in the smaller cells of the cortex, globules of moderate size were found. In the twelfth nucleus the appearances were exactly similar to those seen in the brain of a subject of about 30 or 40 years of age in which small collections of lipochrome pigment are present in some of the neurons, except that in toluidin blue preparations on material imbedded in celloidin no granules were present. In the cerebellum the dendrites of the cells of Purkinje were greatly distended with similar granules.

In unstained sections the lipoid was almost colourless, possessing perhaps the faintest yellowish tint. It coloured blue with Nile blue but was not affected by osmic acid or by the method of Klotz. With Kultschitsky-Pal a few of the granules in some of the cells stained after four days' mordanting but this staining was very feeble. None of the lipoid was anisotropic. It was insoluble in twenty-four hours in acetone, alcohol, chloroform and a mixture of methyl alcohol and chloroform, but with acid alcohol and ether the staining power of the granules in a few of the cells was diminished. As already pointed out, however, the long application of alcohol and ether during the process of imbedding in celloidin removed all the lipoid and in Nissl preparations on frozen sections a variable amount was removed, probably by the xylol.

There was poor myelination of many of the fibres of the white matter and particularly of those association tracts which are not fully developed until several years after birth, but such fibre systems as the optic radiations and pyramidal tracts were normal in their myelin content.

[1] A full report of this case will be published in a subsequent number of this journal.

The glial cells occasionally presented isolated granules of similar properties to those in the neurons and a few small masses of such granules were present in the Virchow-Robin spaces. In the latter situation there were sometimes a few granular corpuscles containing globules and granules of neutral fat, crystals of cholesterin and very occasionally small globules of fatty acid.

Discussion.

In Case V the enormously distended nerve-cells contained a substance of lipoid nature in the form of granules separated by thin protoplasmic bands which by uniting and dividing repeatedly gave rise to an intricate network. The meshes of this network were often smaller and its component strands thicker around the nuclei, while towards the periphery of the cell they were stretched, even to the point of complete disappearance, by the lipoid between them. The lipoid coloured a rosy red or yellow-red with hæmatoxylin and scharlach, and blue with Nile blue, but did not reduce osmic acid. With certain exceptions it was stained by the Kultschitsky-Pal method and this staining was most evident after two to four days' mordanting. The exceptions were seen in some of the smaller nervous elements, chiefly in those of the striatum, which with scharlach gave a much yellower tint than did the large cells; indeed in the nerve-cells the intensity of staining with Kultschitsky's hæmatoxylin diminished as that with scharlach increased. The lipoid was also doubly refractile except in the small yellow cells.

Acetone removed a yellow doubly refractile component and the isotropic residue possessed the solubilities of the phosphatides and cerebrosides, except for a small quantity which required acid alcohol and ether for its removal. In Nissl sections a pale pink diffuse staining indicated the presence of a substance allied to, if not identical with, that constituting the π-granules of Reich. From the mode of preparation of the sections this must have been insoluble in alcohol, ether and xylol.

In Case VI the protoplasmic network was less distinct in most of the cells. When stained with hæmatoxylin and scharlach the lipoid in the large cells was less yellow in colour and that in the small cells more yellow than in the preceding case. It was also less bright in polarized light. In the large cells the lipoid showed the solubilities of a mixture of phosphatides and cerebrosides, but in the small yellow-staining cells a part resisted the solvent action even of acid alcohol and ether. No metachromatic substance was present in Nissl preparations. In other respects there was a close correspondence between the two cases as far as the nervous elements were concerned.

In Case VII not only did the cells show extreme variations in the extent of their involvement, but the lipoid produced by their degeneration differed in many particulars from that in the cases of amaurotic family idiocy. Thus it stained brilliantly with scharlach and was unaffected by the alum hæmatoxylin used in conjunction with that dye. With Kultschitsky's hæmatoxylin most of the granules did not become coloured and when staining did occur it was comparatively feeble. The substance was not doubly refractile and its solubility in the various fat solvents so slow that until celloidin material was examined it was thought to be insoluble. In fact on the whole it more closely resembled the lipochrome pigment seen in the nerve-cells in senile and degenerative conditions than the "lecithinoid" compounds found in amaurotic family idiocy.

Turning to the neuroglia it is seen that in Case V these cells contained different lipoid substances according to their position in the tissues. The satellites often presented inclusions resembling the lipoid of the neurons, but in some its colour with hæmatoxylin and scharlach tended to be more yellow. The wandering elements showed an orange colour and as they approached the vessels there developed in them numerous fine granules of neutral fat which at a later stage coalesced to form small globules. Crystals of cholesterin appeared among the fat globules. Although differing in appearance from the nerve-cell lipoid, the orange-coloured precursor of the neutral fat and cholesterin had similar solubilities, viz., those of the phosphatides, cerebrosides and a substance soluble only in acid alcohol and ether. As regards their contents the granular corpuscles in the white matter were indistinguishable from those in the cortex in a similar position relative to the vessels.

In Case VI the transitional forms between the satellites of the nerve-cells and the granular corpuscles in the perivascular spaces were not nearly so numerous. They were absent in most regions and present in very small numbers in certain areas of the cortex and optic thalamus. Only in the internal capsule were they of frequent occurrence. The neutral fat in the granular corpuscles was mostly in the form of fine granules in the cortex and of larger and smaller globules in the basal ganglia. Cholesterin was less abundant in them. The removal of these substances with acetone left a residue colouring orange with scharlach which was insoluble in alcohol, partly soluble in chloroform and almost entirely so in acid alcohol and ether.

The neuroglial cells in Case VII only occasionally contained lipoid, but

when present the granules were similar to those in the neurons. A few small masses composed of such granules lay free in the Virchow-Robin spaces, to which they had probably been carried by wandering cells which had subsequently disappeared. Granular corpuscles in the Virchow-Robin spaces showed inclusions of the nature of neutral fat and cholesterin.

Reviewing the three cases just described, there can be no doubt that the first two, though differing in some particulars, exhibit the same morphological and chemical changes, and must be accepted as examples of the same morbid condition. But can the third be included in the series with equal confidence? At first sight the differences between it and the two preceding are so great as almost to suggest a separate and distinct disease and justification must therefore be sought for regarding it as essentially identical with amaurotic family idiocy.

In its clinical aspect the case was typical of that form of cerebral and macular degeneration the onset of which is delayed until early or late childhood and which, presenting the signs of progressive and widespread degeneration of the neurons, proceeds to a fatal termination within a few years. The symptoms and signs of this juvenile type differ in no essential respect from those of the infantile variety and are precisely those which would be expected when the age of the onset is considered. Moreover on referring to the literature it is seen that pathologically the two conditions merge into one another and a study of all the recorded examples shows that there is no such sharp distinction between them as this limited series of cases would suggest. It must therefore be concluded that one disease is being dealt with and that the appearances produced by it vary for reasons which will be considered later.

Before proceeding further, however, it is necessary to discuss the reactions and staining properties of the phosphatides and cerebrosides. According to the table given by Cramer it would seem that these substances do not stain with scharlach but are doubly refractile and that while the former are insoluble in acetone but soluble in alcohol and chloroform the latter are soluble only in chloroform. While not disputing that these are their properties as a group it must be conceded that exceptions do exist.

Maclean [22] for example states that sphingomyelin, which is one of the better known phosphatides, is insoluble in cold alcohol. Ciaccio [6] also evidently does not believe that all cerebrosides are soluble in chloroform, for he advocates the use of a mixture of methyl alcohol and

chloroform for their removal. Secondly, the knowledge of these compounds has been obtained by the extraction of the tissues with fat solvents and subsequent attempts at isolation. But even lecithin is difficult to obtain in a pure condition, although it is present in the tissues in large quantities, and many phosphatides and cerebrosides which occur in smaller amount cannot at present be obtained in a sufficient state of purity to determine their individual properties. Thirdly, if some were insoluble in all reagents used for their extraction, they would on subsequent analysis of the tissue be estimated as non-lipoid nitrogen and phosphorus and their identity ignored. Since it is only by the application of information as to their reactions obtained in this manner to the study of microscopical sections that it is possible to recognize the nature of the lipoid substances in them, it will be seen that bodies may be present the nature of which cannot be stated with certainty.

During the examination of the foregoing cases this problem arose many times. In the account of the products of degeneration in Case I reference has been made to material present after the application of acetone which coloured with scharlach, was not doubly refractile, but was soluble in alcohol, thus having the solubilities of a phosphatide but differing from the recognized members of the group in its reaction with scharlach and its isotropy. In Case II, in addition to a small amount of doubly refractile material soluble in alcohol but not in acetone which, on account of the bright pinkish colour it assumed with scharlach, was considered to consist of cholesterin esters, there remained after acetone an occasional thin, doubly refractile ring staining brownish with scharlach and dissolving in alcohol. Here again was a substance resembling the phosphatides except that it stained with scharlach.

In Case IV there was a scharlach-staining isotropic substance, insoluble in acetone, partly soluble in alcohol and in chloroform and entirely soluble in acid alcohol and ether. In Cases V and VI similar difficulties in classifying some of the lipoid were encountered. Finally the normal myelin, which is composed mainly of cholesterin, phosphatides and cerebrosides, usually shows after the action of chloroform a small residue which stains with scharlach and is soluble in acid alcohol and ether.

The scharlach-staining material soluble only in acid alcohol and ether might be thought to be a compound of lipoid with protein which is split up by the action of the acid, thus allowing the liberated lipoid to dissolve; and it is known that the phosphatides and cere-

brosides readily enter into protein combination. But lipo-protein compounds do not stain with scharlach. Moreover these substances often showed a progressive solution in the fat solvents, part being soluble in alcohol, more in chloroform, still more in a mixture of methyl alcohol and chloroform and all or nearly all in acid alcohol and ether. In certain cases also, e.g., in some of the granular corpuscles in Cases IV, V and VI, the appearance of the lipoid remaining after each of these solvents was the same, when stained by scharlach, and variation occurred only in the amount in each section. These facts suggest that the various fractions are intimately related.

Now the reaction with scharlach is not a chemical one which might be expected to occur with all members of a group of substances which are united by reason of their chemical constitution, but is due to a simple solution of the dye-stuff in the lipoid. It does not appear unreasonable, therefore, to suppose that some phosphatides and cerebrosides may stain with this dye, although others do not, and any material having the solubilities of these compounds probably belongs to this category. As has been shown, the fractions of lipoid which are soluble only in acid alcohol and ether have exactly the same appearance as those soluble in alcohol or in chloroform, and when present are invariably associated with them. This seems to be strong evidence that they are closely allied bodies even if they do not actually belong to the same groups.

To approach the question from another standpoint, it may be asked what their nature is if they do not belong to the class of phosphatides and cerebrosides. They have few points of resemblance to the neutral fats, to the fatty acids or to the cholesterin compounds. Sulpho-lipoids exist but in very minute quantities, and beyond the fact that they are related to the phosphatides nothing is known of them or of their reactions. So that although absolute proof is not forthcoming, such evidence as there is suggests that the bodies under discussion are to be regarded as belonging to the phosphatides and cerebrosides.

Returning now to the cases of amaurotic family idiocy, the part played by these substances can be appreciated. In the larger nerve cells in both cases they formed the majority of the lipoid and coloured a purplish red with alum hæmatoxylin. In Case V a doubly refractile substance or substances staining yellow with scharlach and soluble in acetone was present in small amount, and probably consisted of cholesterin and its esters. The metachromatic staining of Nissl sections indicated the existence of substances similar to those forming the

π-granules of Reich which are generally accepted to be a mixture of various phosphatides and cerebrosides. In Case VI there was also a small amount of a doubly refractile substance soluble in alcohol but not staining yellow with scharlach, and this probably consisted of cholesterin alone, the scharlach-staining esters being absent.

The striking resemblance of the contents of these neurons to normal myelin cannot be ignored, and while this may be purely accidental, it seems not impossible that the formation of the latter may be due to factors which when operating in one region give rise to the very necessary insulating or protective sheath of the axis cylinders, though in another they produce the grossest abnormalities.

The satellites surrounding the nerve cells possessed similar contents, and it appears very much more probable that these inclusions had been absorbed from the neurons than that they were due to a primary affection of the neuroglia by the morbid process. In the granular corpuscles it was possible to trace the successive stages in the breaking down of these lipoids. The reaction with alum hæmatoxylin was lost and replaced by one with scharlach; at the same time a part of the lipoid became insoluble in chloroform, being soluble only in acid alcohol and ether. Cholesterin separated out in crystals and fine granules of neutral fat appeared which later coalesced into small droplets. In the granule cells in the Virchow-Robin spaces these appeared to be the only inclusions, but after their removal with acetone a quantity of their precursor was still visible. The apparent absence of fatty acids during the breaking down of phosphatides and cerebrosides can only be explained by assuming that the process was sufficiently slow to enable them to be converted into neutral fats as rapidly as they were produced.

The appearances detailed above were those which predominated in most regions of the brain. As already described, however, other nerve cells, viz., some of the smaller cells and particularly those of the striatum, showed a lipoid of a somewhat different nature. In Case V this stained yellow with scharlach and was not doubly refractile, but its solubilities were the same as in the larger elements. In Case VI not only did the contents of these small elements stain bright yellow with scharlach and remain dark in polarized light, but they did not completely dissolve even in acid alcohol and ether. In both cases they stained poorly or not at all with the Kultschitsky-Pal method. Here there is evidence of some difference in the phosphatides and cerebrosides, causing them to stain with scharlach but not with hæmatoxylin and to become insoluble in various reagents. Is this difference due to a conversion of the lipoid

found in the large cells into the type found in these small elements by a process similar to that at work in the granular corpuscles, or was there from the commencement some slight variation in the morbid process resulting in the formation of a lipoid of somewhat different nature? The answer to this question seems to be found in a study of Case VII.

In this case of cerebro-macular degeneration the lipoid stained brightly with scharlach but not with alum hæmatoxylin, while with Kultschitsky-Pal its reaction was very feeble or entirely absent. It was very insoluble, and for a considerable time resisted solution in all reagents except xylol, in which a part dissolved in the process of mounting preparations of frozen sections, It was not doubly refractile. Although satellitosis was common, the glial cells only occasionally contained lipoid; perhaps the insolubility of the substance did not permit its transference to these elements.

Now although many cells showed only slight affection and contained but small amounts of lipoid, being obviously in an early stage of involvement, the characters of the lipoid were the same throughout. It would therefore seem probable that the differences between it and that seen in the large cells of Cases V and VI were present from the commencement, being due to a modification of the morbid process responsible for their production. Applying this conclusion to the question raised above, it also appears likely that the lipoid in the small cells of Cases V and VI, which, differing in certain respects in the two cases, possessed properties intermediate between that in the large cells of these cases and that in the case of cerebro-macular degeneration, represented two links between these extremes and that here again the differences in its reactions existed from the beginning.

The chief difference between amaurotic family idiocy and cerebro-macular degeneration lies in the rapidity of progress of the two diseases. Whereas in the former the duration is usually to be stated in months in the latter the patient often lives for a number of years. Moreover, the close resemblance of the lipoid in the case of cerebro-macular degeneration to the lipochrome pigment of senile and degenerated nerve cells, which is of extremely slow production, has already been mentioned and a table has been compiled showing the relation of the lipoid seen in amaurotic family idiocy, in cerebro-macular degeneration and in senile nerve cells. Except for the reaction with Kultschitsky-Pal stain the table shows a perfect gradation in the properties of these substances according to the rapidity with which their formation occurs. The

inevitable conclusion is that each of these degenerations is essentially the same and that the differences that exist are due solely to the acuteness or chronicity of the process. In amaurotic family idiocy cerebrosides and phosphatides are liberated in a readily soluble form and possess staining properties more or less typical of the groups. In cerebromacular degeneration and in the senile nerve cell they are so altered as to become insoluble in the fat solvents and to stain with scharlach. But between the products of degeneration in amaurotic family idiocy and the lipochrome pigment there exist substances of intermediate properties, some near one end of the scale and some near the other, and a complete chain unites the two extremes.

	Amaurotic family idiocy			Cerebro-macular degeneration	Lipochrome pigment
	Large cells	Small cells			
		Case V	Case VI		
Colour.. ..	Colourless	Colourless	Colourless	Possibly a very faint yellow in some cells	Yellow
Alum hæmatoxylin	Rosy red or purple	Not affected	Not affected	Not affected	Not affected
Kultschitsky's hæmatoxylin	Maximum 4th day	Feeble or not at all	Feeble or not at all	Usually negative	Maximum 2—5 days
Scharlach ..	Rosy red with hæmatoxylin and scharlach	Pale yellow	Yellow	Yellow-orange	Orange-red
Osmic acid ..	Unaffected	Unaffected	Unaffected	Unaffected	Brownish-black
Osmic acid after chromication	Unaffected	Unaffected	Unaffected	Unaffected	Brownish-black
Double refraction	None	None	None	None	None
Nile blue ..	Blue	Blue	Blue	Greenish-blue	Blue
Solubilities ..	Case V most soluble in alcohol, more in chloroform, all in acid alcohol and ether. Case VI most soluble in alcohol, all in chloroform	Most soluble in alcohol, more in chloroform, all in acid alcohol and ether	Most soluble in alcohol, more in chloroform, but not completely soluble even in acid alcohol and ether	Soluble with great difficulty in alcohol and ether. In 24 hours soluble in none of the reagents	Insoluble in all reagents

N.B.—In the case of amaurotic family idiocy the presence of cholesterin and its esters (which were in small quantity) and the reactions due to them have been ignored.

Schaffer [31] has arrived at similar conclusions, but his views are in direct opposition to those of Dide, Guiraud and Michel [8], who

considered that the lipoid in their case of cerebro-macular degeneration bore no relationship to lipochrome pigment. Unfortunately in many of the cases recorded in the literature no account of the solubilities of the lipoid is given and in addition the staining methods used have in most instances been few. Even where a fairly full investigation has been made, each writer has used different staining methods and consequently comparison is very difficult. As far as they go, however, the results are in accord with those obtained in the present series of cases and emphasize the fact that all gradations occur between the lipoid in amaurotic idiocy, in cerebro-macular degeneration and in the senile nerve cell.

The nature of the products of degeneration having been dealt with, a brief space must be devoted to the question of their origin. The views of Rosenfeld, and of Fischer and Hooker, have already been quoted as showing the tendency of modern thought in this direction and their application to pathological conditions of the nervous system is a matter of considerable interest.

There can be no hesitation in affirming that the neutral fat globules seen in the degenerative conditions that have been discussed were not due solely, if at all, to a rendering visible of fat already present.

Their development has been followed through successive stages and their origin from the disintegration of more complex lipoids established. This does not, however, dispose of the problem, for it now remains to be seen whether the precursors of the fat are present as such in an emulsified form, or whether they are produced from the breaking down of protein.

In the normal myelin, the lipoids probably exist as such, for not only do they stain with various fat stains, but they can be dissolved in successive fractions, according to their individual solubilities, by the application of fat solvents. The percentage of lipoid found in the white matter is so high that when the purely plasmic structures such as neuroglia cells are taken into consideration, it is obvious that in the myelin itself there can be but little protein and certainly not sufficient to unite chemically with all the lipoid substances that form its bulk. Again the fact that the lipoids in the myelin sheath stain with fat stains is a point against the existence of an emulsion, for, as Fischer and Hooker state, the emulsification of a fat leads to the loss of its staining reactions. Also it is questionable whether sufficient protein exists in the myelin to form an hydrated colloid of sufficient concentration to emulsify the lipoid.

In the cell protoplasm, on the other hand, no lipoid is detectable with fat stains in the normal condition and therefore, if any is present, which cannot be doubted, it is either in chemical combination with protein or in a finely divided condition in an emulsion. In the cases of neuronic degeneration that have been investigated, the course of the disease has been comparatively or absolutely slow, that is to say it has occupied at least a period of months. Now an emulsion once formed offers considerable resistance before it is broken and gross changes in the concentration of the hydrated colloid forming the continuous phase are necessary before the lipoid separates out. When, however, the conditions are such that an emulsion is no longer possible, the breaking takes place throughout and with relative rapidity. It cannot be supposed that in such conditions as amaurotic idiocy, cerebro-macular degeneration and pigmentary degeneration of the senile nerve cell, the lipoid is produced suddenly at a given stage: the degeneration and the accumulation of lipoid must take place slowly over a period of months or years. It must, therefore, be concluded that the phosphatides and cerebrosides found in these conditions have been liberated from chemical combination with some other cellular substance and as it is known that they unite readily with protein, it may be assumed that they exist in the form of lipo-proteins.

In conclusion I wish to thank Dr. J. G. Greenfield for his unremitting interest and valuable advice during the progress of this research.

APPENDIX.

Anderson's Modification of the Kultschitsky-Pal Method.

Sections are cut by the freezing microtome and are placed in the following solution in which they remain for twenty-four hours at 37° C.:—

Weigert's primary mordant	90 c.c.
2 per cent. solution of calcium hypochlorite (commercial bleaching powder, or "chloride of lime")	10 „

They are then transferred to Weigert's "Gliabeize" solution for ten minutes. After a rapid wash in distilled water they are placed in the following hæmatoxylin solution for one hour at 50° C.:—

Hæmatoxylin	0·5	gm.
Absolute alcohol	10	c.c.

Mix well and add—

2 per cent. calcium hypochlorite	3	„
Glacial acetic acid	3	„
Distilled water ... ... to	100	„

From this they are transferred directly to Müller's fluid and after ten minutes to tap water. Differentiation is carried out in the usual manner by Pal's method.

The results obtained by the Kultschitsky-Pal method described above agreed in general with those of Lorrain Smith and Mair [17] who used Weigert's original method. Different lipoid substances stained after different periods of mordanting, and although this process was not carried beyond the sixth day, even at this time the lipoids which had stained soonest had already faded considerably. The normal myelin coloured darkly on the first day of mordanting and even more darkly on the second. After four days considerable fading had occurred except in Case IV, where it still stained darkly on the fifth day. This case had been preserved in formalin for nearly two years and it is possible that the long action of the fixative was responsible for the continued staining, but similar appearances were not seen in Cases V and VI which had been subjected to its action for at least twelve months. The lipochrome pigment, on the other hand, possessed little or no affinity for the hæmatoxylin on the first day; on the second day it still stained poorly, but on the third, fourth or fifth days a dark coloration was seen. The other results of this method were briefly as follows:—

Case I.—The globules consisting mainly or entirely of myelin stained at the same time as the normal fibres. The fatty acid which was mixed with a small amount of neutral fat stained best on the second and third days, its colour being then a medium violet. The few crystals of pure cholesterin did not stain.

Case II.—The myelin globules stained at the same time as the normal sheaths. The neutral fat stained feebly on the first day, better on the second and darkly on the fourth. The crystals of pure cholesterin were not stained nor was any doubly refractile material visible, after staining, among the products of degeneration. Other lipoids, e.g., fatty acid, phosphatides, &c., were in small amount and it was impossible to determine their reaction.

Case III.—The neutral fat stained poorly on the first day, moderately on the second and well on the fourth. The crystals of cholesterin did

not stain and no doubly refractile material other than the myelin was left in these sections.

Case IV.—The neutral fat stained in increasing intensity from the first to the fifth days. The cholesterin was not mordanted. Phosphatides and cerebrosides were in small amount and could not be recognized with certainty.

Case V.—The contents of the large cells stained lightly in one day, darkly in two days and very intensely in four days, thereafter commencing to fade. The small cells of the striatum coloured feebly or not at all, their staining reaching a maximum on the second day and continuing unchanged until the fourth day, after which they began to fade. The contents of the granular corpuscles in the white matter were darkest on the third day, but around the vessels where there was a greater proportion of neutral fat the maximum was not reached until the fifth day. The cholesterin crystals did not stain.

Case VI.—The results were similar to those in the preceding case except that the staining of the large neurons was not so intense.

Case VII.—The lipoids did not stain with this method except in the case of a few granules which coloured feebly on the fourth day.

Summarizing these results it will be seen that the farther removed the products of degeneration from normal myelin the longer is the period of mordanting necessary before they acquire their greatest affinity for hæmatoxylin. Thus neutral fat requires four to six days mordanting and stains darkly at a time when the myelin has become overmordanted and has faded considerably. Fatty acid occupies an intermediate position and stains best on the second and third days. Cholesterin did not colour in any of the above cases. Lipoids present in small amounts cannot be recognized with certainty, and in the case of mixtures the period and extent of staining depends on the substances present and their relative proportions.

Lorrain Smith and Mair state that while cholesterin in a pure condition does not stain it does so when mixed with triolein or oleic acid. The latter part of this statement was not confirmed by the present investigation, for no doubly refractile material was seen after staining in the degenerated areas even at the period of maximum staining, and it must be concluded that if cholesterin did contribute to the reaction its union with hæmatoxylin had destroyed its property of double refraction. If cholesterin does react differently according to the lipoids with which it is associated the value of the method is largely abolished. On the whole it appears that the value of the method lies

in its ability to show the stage to which degeneration has progressed, and that alone it cannot be used for determining the exact nature of the lipoids present. It is also useful as a means of demonstrating the granules in the neurons in amaurotic family idiocy.

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MICROSCOPICAL OBSERVATIONS ON THE CIRCULATION OF THE BLOOD IN THE CEREBRAL CORTEX.

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I.—Introduction.

The present investigations had as their origin an observation made by Professor Sherrington while engaged in mapping out the motor area of the cerebral cortex of monkeys.

He had noticed that if the superficial cortex exhibited a reddish flush the preparation was active, but if, as sometimes was the case, a somewhat yellowish colour appeared there was great difficulty in eliciting responses to electrical stimuli.

He suggested that the methods used by Krogh might be applied to an investigation of the cerebral circulation.

II.—Methods employed.

Most of the experiments were performed on cats, but the main findings were confirmed on rabbits. One monkey was also used.

The usual method of anæsthetization was by means of subcutaneous injection of chloral hydrate. For a cat of 2,000 gm. 8 to 10 c.c. of a

20 per cent. solution in distilled water was sufficient to produce an even anæsthesia lasting several hours.

Anæsthesia by this method was complete in about an hour. In some animals Cheyne-Stokes respiration was produced.

Occasionally during the operative procedure a small amount of ether was given in addition, but the chloral anæsthesia was found to be adequate for the subsequent manipulations.

The main results have been confirmed in animals which were anæsthetized by either a mixture of two parts ether and one chloroform, or ether alone. When this latter method was used the anæsthetic was administered through a tracheal tube connected to a Woulfe's bottle. In rabbits urethane was occasionally used. The operation employed in all cases except where specially stated was as follows :—

The animal was placed on its belly with head extended. A longitudinal cut was made over the convexity of the cranium in the middle line, this being of sufficient length to give free access to the bony skull. The skin was then retracted by clip weights and the skull freed from attached muscles, any bleeding being controlled by the application of moist hot cotton wool swabs. A trephine opening was then made in the parietal region about 3 mm. from the middle line. It was found expedient to use the trephine without a pin owing to the danger of forcing small spicules of bone from the inner table of the skull through the pial vessels. The plate of bone was removed and the dura laid bare. All bleeding from the diploë can usually be stopped by the application of warm moist cotton wool swabs. Occasionally plasticine had to be used, rubbed into the bleeding spot, but this is better avoided as small pieces may press on the cortex and disturb the circulation. It was found useful to remove the trephine when the diploë was reached and bleeding had commenced, and then smear plasticine into the cut ; this was then ground into the cut surface by further trephining.

The dura mater, supported on the point of a needle, was then incised at one point by sharp scissors. With fine forceps and scissors a cruciate incision was made and the cut dura turned back. This turning back was sometimes facilitated by making more radial cuts. By this means bleeding from cut vessels in the dura mater can be controlled, whereas if the dura be cut entirely away there is a tendency for oozing over the field of vision to occur from the cut edges.

It is essential to have complete hæmostasis from the diploë and if possible from all other points before opening the dura, as the accumulation of blood on the pial surface necessitates harmful interference to

remove it. The field of view is obscured if blood has been allowed to cover it previously. Bleeding from accidentally punctured pial vessels, especially during stimulation by fine glass rods, was at times difficult to stop. Cotton wool pledgets usually sufficed, but in event of failure a small piece of muscle applied over the bleeding spot was always successful.

For observation the animal was placed on a warm table and held in a clamp attached either to its upper or lower jaw. If the trephine hole subsequently required enlargement parrot-billed forceps were used. The cortex was kept moist by applying warm saline swabs, but in most cases the oozing of the cerebro-spinal fluid was found to be sufficient.

For illumination a 100 c.p. Pointolite lamp was employed; this was attached to a stand so that the beam could be focused obliquely on to the skull opening. No heat filter was necessary, as a thermometer placed at the focus did not register more than 20° C. Most of the experiments were conducted before the use of a light filter was considered, but the use of a green filter, such as the Wratten B, greatly diminishes eye strain and produces the picture of black vessels against a green ground, thereby greatly increasing the clarity of the picture.

The microscope employed in most of the experiments was a Spencer dissecting, giving stereoscopic vision. The body was fitted to a laboratory-made stand whereby a greater range of movement was obtained. The magnifications obtainable were 20, 50, 74 and 100 diameters.

The method of vital injection was employed for some purposes. For this operation the abdominal aorta was first tied as high up as possible and then loops passed round both carotid arteries, internal jugular veins (when present) and external jugular veins. A thick cord was also passed round the vertebral column high up, in such a position that, on tightening, the vertebral arteries were occluded.

The thorax was then rapidly opened and 5 c.c. of blue or black indian ink injected into the left ventricle. This ink was then carried round in the circulation. When after the lapse of ten to fifteen seconds it was judged that the ink had circulated sufficiently, the carotid, jugular and vertebral vessels were quickly tied. The upper portion of the skull was then removed and the head separated. The whole head was then fixed in 5 per cent. formalin, the brain after fixation being extracted from the skull.

III.—Description of the Appearances presented by the Cerebral Cortex.

One of the difficulties inherent in observation of the cortex with a microscope is the pulsation imparted to it both by the heart-beat and the respiration. This pulsation limits the degree of magnification for prolonged observation to about 50 diameters, but for a short time, to view some particular phenomenon 100 diameters magnification can be used. For the same reason exact measurements of the sizes of arteries and veins cannot be made.

The general first impression is that of a network of vessels spread over a pinkish background. The colour of this background is entirely due to the vessels contained within the cortex, as was shown by a vital injection. If blue ink be used it is found that the whole cortex presents a uniform bluish colour, which is not impaired by stripping the pia.

Sometimes the pink colour appears to be not uniform, lighter patches occurring in some places. This is especially so along the arterial trunks which sometimes appear to be on a narrow strip of white background. This, however, is an optical phenomenon due to the angle of incidence of the light upon the supporting tissue of the pia; the light patches can be made to alter their position by alteration of that of the source of light.

The network of vessels on closer inspection can easily be divided into arteries and veins.

The *veins* are much the more numerous and form a very richly anastomosing network. They present a flat contour in contrast to the full rounded appearance of the arteries, are more irregular in size and more sinuous in course than the arteries. The majority of the emergent veins come from the depths of the cortex in an oblique direction, but quite large numbers come up perpendicularly to the surface and so appear as dark round spots.

The blood may be collected into quite large veins which again break up into smaller vessels, receive fresh side branches, and again reunite; anastomotic circles are quite common.

Another common appearance is for two large emergent veins to be connected at their points of emergence by a very fine, perhaps long, intrapial vein. A usual appearance is for a leash of small, obliquely emergent venules to converge to enter a large vein as it leaves the cortex for the pia.

The *arteries* are less numerous, less branching and present a more fully rounded appearance than the veins.

They also form anastomotic circles, but not so richly as the veins. The most striking appearance, however, is the number of small and large red dots scattered along the arterial trunks. These are the arteries seen in cross section which dip perpendicularly into the brain substance. The perpendicular direction is much more common for the arteries than the veins. Occasionally from the sides of the arteries vessels of capillary size can be seen passing somewhat obliquely into the cortex.

Another peculiarity is that some, but not all, arterial branches arising from a large artery present at their origin an annular constriction, which results in the portion of the artery immediately peripheral to a junction being of greater diameter than the junction itself. It is possible that the annular constriction is of the nature of a sphincter, but this region does not exhibit an increased irritability to any form of stimulus.

The large arteries are always superficial to the large veins, and this relationship persists till the subdivisions are quite small. The number of perpendicularly dipping vessels seen in a normal cortex is limited by the fact that the overlying layer of blood in the larger arteries and veins obscures the mouths of the vessels passing from the under surface. If the circulation be stopped by killing the animal, e.g., by chloroform, numbers of round dots become visible along both arteries and veins which represent the orifices of the perpendicular vessels,

Vessels of *capillary* size can be seen both going from the arteries and, more numerously, entering the veins.

The flow of blood can be quite easily observed in the venous capillaries and the smaller and moderate-sized veins. It cannot normally be observed in the arteries or large veins.

The flow in the veins.—In the smallest venous radicles the appearance is that of a succession of "beads" of massed corpuscles, the intervals between which are filled with clear plasma. That this beaded appearance in the flow is not inflammatory is indicated by the fact that it can be noted in the most freshly prepared cortex, which has been subjected to practically no mechanical interference; it can be observed to keep the character unchanged for hours; if it were inflammatory in nature one would expect it to exhibit progress towards stasis.

This phenomenon of beaded flow is also to be seen in the skin vessels of albino rabbits which have been subjected to no injury. The flowin the medium-sized veins exhibited pulsatile movements synchronous with those of the heart-beat, this pulsatile flow being accompanied by slight expansion and shrinking of the veins.

In some preparations it has been noticed that as the arteries expand the veins lessen in diameter, and this occurs synchronously with the heart-beat. This probably exhibits the normal relationship in the vessels, for the brain being enclosed in a rigid case, with the accompanying restrictions of flow by reason of this, as the blood is forced into the arteries the veins are compressed to make way for this increased flow.

A gradual swelling and subsidence in the larger veins synchronous with expiration and inspiration respectively is noted.

When the stream from a small vein enters a larger, especially when the blood current is slow, the identity of the two streams can be traced in the larger vessel for considerable distances, a zone of clear plasma separating the two columns of corpuscles. In this way, by an accession of several tributaries, a large vein exhibits a longitudinally banded appearance.

The usual variability of the direction of flow presented by a venous anastomosis is present. This variability appears to be entirely dependent on relative pressures in the various venous branches, as it is independent of variation in size of the veins. In some veins, for instance, a column of blood may become stationary and massing of corpuscles may occur, but after the lapse of a few seconds the flow may be reestablished, to be altered in direction a moment or two later.

Another appearance is that of a length of vein apparently homogeneous having a blood-flow which starts from some middle point and goes in opposite directions. This appearance is due to the fact that a perpendicular emergent vein branches in a "T" fashion and is being observed from above in the vertical plane.

Flow in the arteries.—A pulsation, synchronous with the heart-beat, is found in the largest arteries but disappears before the finest arterial branches are reached. This is best observed at a sharp bend, in which situation the convex side becomes increased in convexity during systole.

IV.—The Effects of Stimulation.

(*a*) *Mechanical.*

The effects of mechanical stimulation were obtained by pushing against or rubbing the vessels by fine glass needles. The vessels of the cat were found to offer considerable resistance to rupture by such treatment, but those of the rabbit are extremely delicate and far more vulnerable.

By this means it was found that all arterial branches, from the largest to the smallest visible, reacted to a moderate or vigorous stimulus by a powerful contraction, localized to the point stimulated.

In the matter of this localization it was found impossible, owing to the cerebral movements, to stimulate the smaller vessels precisely at one point so as to obtain contraction. For this reason contraction was spread over some distance, but never beyond that compassed by the fluctuations of the stimulating needle.

The larger arteries exhibited an annular contraction which was not propagated away from the point of stimulus.

With great care it is quite possible in a large vessel so to stimulate that only one side of the vessel wall, that which is directly under the needle, contracts. The duration of such contractions is from four or five seconds to ten minutes, depending on the vigour and the length of the initial stimulus. Occasionally in a large artery at the point stimulated a contraction occurs, while immediately on either side a dilatation is present. These two narrow bands of dilatation rapidly give way, in four to five seconds, to constriction, which blends with the already constricted portion. The smaller arterial branches can be made to contract to obliteration.

With gentle rubbing a localized dilatation can be produced in the arteries, but this is much less easy to elicit than constriction, in fact most efforts at producing dilatation resulted in contraction, but occasionally one was successful in producing a dilatation.

The veins show no reaction whatever to a mechanical stimulus. This lack of reactivity is shared by both large and small veins.

The capillaries given off by the arterial branches possess the power to contract to obliteration with a vigorous stimulus; a gentle stimulus will result in a dilatation, as is evidenced by the greater flow of corpuscles which the capillary accommodates. The capillaries flowing into the veins do not, however, exhibit this reactivity; even with the most vigorous stimulus contraction failed to appear. Mechanical alteration could be produced which gave the appearance of dilatation, but it seemed clear that there was no true active dilatation of the venous capillaries.

In cases where the artery is ruptured it can be seen, after bleeding is stopped, that it has contracted at the point of rupture and for a considerable distance on either side of it. In this connection, however, it was found that the most efficacious way of arresting cortical bleeding was the application of a small piece of muscle to the bleeding point. It

would seem that the contraction is not sufficiently powerful to stop bleeding completely, but must be reinforced by clotting.

It was thought desirable to try the reactivity of the vessels in the region of the medulla as all of the preceding experiments were confined to the cerebral cortex.

The following operation was employed for exposing the anterior surface of the medulla.

Both the carotid arteries were tied low down in the neck and a tracheal cannula inserted. The trachea and the œsophagus were cut through above the insertion of the cannula, and in the middle line the dissection was carried down to the base of the skull. The base of the skull between the two large inferior air sacs was cleared of muscle as far forward as possible and back as far as the anterior atlanto-occipital membrane. An incision was made in this membrane which occasioned some bleeding, but this was eventually stopped. With nibbling forceps the skull between the two air sacs was removed—the nibbling starting at the lip of bone to which the atlanto-occipital membrane was attached.

On the removal of the skull the dura mater remained exposed. This was incised longitudinally in the middle line and turned back, thus exposing the basilar artery and the anterior surface of the medulla and pons. At the end of the operation the breathing and the circulation remained normal.

Mechanical stimuli to the vessels here exposed resulted in the same appearances as those presented by the cortex under similar treatment.

It is found that, after the exposure of the cortex to the air for about two hours, the arteries lose their ability to contract and react only to very vigorous stimuli or not at all. It is thought that this result was due to the onset of inflammatory phenomena, as examination of histological sections showed a moderate collection of polymorph leucocytes in the vessels and a slight degree of diapedesis into the surrounding tissue.

(*b*) *Electrical Stimuli.*

A unipolar stigmatic electrode was used. This electrode was constructed from an entomological pin fused into the end of a glass tube and connected by a flexible wire with one pole of the secondary coil of an inductorium. The other electrode was a brass plate fixed to a hind foot. A rapid succession of faradic shocks could thus be applied to a small stretch of artery.

By this method it was found that the branches of the arterial tree which reacted to mechanical stimuli also reacted in a similar way to electrical; that is, there was a localized contraction at the point stimulated, allowance being made for the slight spread of current around the electrode.

The degree of contraction, and the duration of the stimulus before the effect was noticed, varied closely with the strength of stimulus employed. The degree of contraction varied from a slight constriction to complete obliteration, the latter being especially marked in the smaller arteries.

Sometimes at the point stimulated, especially when the stimulus was strong, a vigorous contraction resulted with a dilatation on either side, with again rings of contraction. The dilated portions gradually became propagated away from the point of stimulus to blend with the normal artery, the whole area then exhibiting reaction being in a state of contraction. In some cases, however, the varicose condition persisted.

The latent period varied from fifteen or twenty seconds to half or one second. The duration of contraction varied from two or three minutes to hours—the longest time of contraction observed being two and a half hours, in which case the artery was still contracted at the conclusion of observation.

Sometimes with weak stimuli a dilatation only was produced at the point stimulated.

In some animals portions of arteries could be obtained in which no effect was manifested, though a reaction of contraction existed on either side of the refractory portion.

In some animals and some arteries it was found that portions of arteries which to an initial stimulus react with contraction also exhibited this refractory condition with a repeated stimulus after recovery from the first. This lack of reaction occurred whatever the strength of stimuli, but was only observed at certain points on an artery. After an interval of about fifteen minutes, but the time is very variable, the previously refractory portion of the artery will again contract to stimuli.

The arterial capillaries also react by contraction, but the venous capillaries and the veins do not react at all.

Medulla.—The anterior surface exposed as described above was stimulated; the vessels reacted in a way precisely similar to those of the cortex.

In connection with the observations on electrical stimuli the following interesting phenomenon was observed:—

With a strong current and the interrupter working at about thirty per second gas bubbles could be seen to rise round the stimulating point. In a monkey, which had been used successfully to demonstrate the cortical motor area, the point of the needle was observed during the passage of precisely the same strength of current as was used to elicit the movements. With this strength of current bubbles were generated at the point of the needle. This fact shows that the amount of disturbance which a cortical motor cell must undergo before producing a muscular movement (to artificial stimuli) is much greater than is generally supposed.

(*c*) *Thermal Stimuli.*

Heat.—The effects due to heat were evoked by the application of cotton wool pledgets soaked in warm saline, or by dropping warm saline from a fine pipette. It was found that the application of saline at a temperature of 45° to 47° C. resulted in arterial constriction, but here again the individual susceptibilities of the arteries were markedly different, some almost contracting to obliteration, others remaining unaffected.

Temperature of 40° C. caused arterial dilatation. In order to demonstrate dilatation by this or other agents producing dilatation a moderate degree of constriction was produced mechanically, and if this was rapidly removed by the agent being tested, it was assumed that this agent had the property of dilating the vessels.

The veins showed no reactions.

Cold.—The application of cold was practised by dropping ice-cold saline from a pipette, or by the direct application of ice to the cortex. The application of a piece of ice for fifteen to twenty seconds resulted in a moderate degree of contraction of the arteries—the smaller being especially affected. The vessels also showed a great variability to this method of stimulation, some reacting powerfully and repeatedly, others being scarcely affected; or a particular piece of an artery only might contract, while portions on either side were quite unresponsive. The cortex in some cases lost its flush and some of the venous channels disappeared; the flush returned and the venous flow was fully re-established on warming.

V.—Effect of the Application of Drugs.

Adrenalin.—Adrenalin in solution varying in strength from 1 : 1,000 to 1 : 10,000 was applied diffusely by means of a small glass pipette, or on a fine glass rod when a small portion of an artery was to be tested.

In every animal and under all conditions the local application of adrenalin failed to produce any contraction of the arteries at all. In some cases a slight dilatation was noticed.

In one experiment a portion of an artery was caused to contract by mechanical stimulation: to this contracted portion a drop of 1:1,000 adrenalin was applied. Immediate dilatation of the contracted portion resulted. Contraction recurred spontaneously after five seconds, but the addition of another drop of adrenalin again caused dilatation. In another animal, however, the experiment failed.

In many cases after the application of adrenalin the arteries were found to be irresponsive to mechanical stimuli, however vigorous, whereas before the application they had reacted vigorously.

Medulla.—By the method already described the anterior surface of the medulla was exposed. The application of adrenalin caused no contraction of any arteries.

Floor of the fourth ventricle.—The animal was decerebrated in a Sherrington decerebrator. The tentorium cerebelli was removed with nibbling forceps and the skull covering the upper portion of the cerebellum was similarly removed, starting from the occipito-atlantal membrane. The cerebellum was then dislocated forwards through the opening in the tentorium cerebelli. The remainder of the roof of the fourth ventricle was removed and the bleeding stopped by the application of moist saline pads.

On observing with the microscope it was then seen that no vessels course actually on the surface of the fourth ventricle, but are covered by a thin layer of white matter. All vessels in such a field appear to be of a venous character, but vessels of capillary size were seen.

The application of adrenalin had no effect on the vessels, or on the flow of blood observable in them.

Effects of the injection of adrenalin into the blood-stream.—In the case of the cortex the only visible effect was an increase of the speed of flow—no contraction. The cortex was also bulged through the trephine opening, indicating that more blood was being forced into the cranium, increasing the bulk of the brain contained in it. A glass window in one experiment was fixed in by means of collodion. Though the joint was not perfect a nearer approach to physiological conditions was obtained. (A method for making a perfect joint is to be described later.) In this case also the only effect was an increase in the speed of the blood-stream. The same effect was seen in the medulla.

Another method employed for testing the effect of adrenalin depended

on the "vital injection" of indian ink (black or blue "Pelican" brand). The aorta was tied in the abdomen so that the arterial supply to the liver and spleen remained intact. The thorax was then rapidly opened and 5 c.c. of ink injected into the left ventricle of the still beating heart. The experiment was repeated on a second rabbit of the same size and age in exactly the same way, the ink, however, being mixed with adrenalin, so as to be of strength in adrenalin of 1 : 10,000. The brain injections of these two animals were then compared.

In the first case the liver and spleen were well injected, the brain moderately; in the second the injection of the liver and the spleen was patchy, but that of the brain good.

Though not of itself conclusive evidence of the non-reaction of the cerebral vessels to adrenalin, the interpretation seems justified that in the latter case the adrenalin had caused constriction of the vessels supplying the liver and spleen, but the only effect on the cerebral vessels was to fill them more adequately owing to the higher blood-pressure due to arterial constriction in other parts, and more vigorous action of the heart.

Control experiments with adrenalin were done on the vessels of the mesentery. With these the application of one drop of 1 : 1,000 adrenalin resulted in extreme constriction, which was rapidly propagated peripherally.

Intravenous injection of 1 c.c. of 1 : 10,000 solution also resulted in a very high grade of constriction. The mesenteric arteries presented a beaded appearance when they first began to contract. It was thought that the first parts to contract might be associated with the points of junction between the splanchnic nerves and the muscle of the arterial wall.

Pituitrin.—The effect of the local application and intravenous injection of pituitrin was tried in the same way as for adrenalin. In no experiment was any arterial constriction observed.

Barium chloride.—Five per cent. barium chloride solution caused marked contraction, but solutions of less strength did not have very pronounced effects. The same statement applies to the medullary vessels.

Nitrites.—Three per cent. sodium nitrite caused dilatation, but this agent is not very powerful. A solution made by shaking amyl nitrite with water produced a very marked dilatation of all arteries. This solution is capable of producing dilatation of portions of arteries contracted mechanically or electrically.

Strychnine.—The effects of the local application of strychnine were elicited with the sulphate (2 per cent. approximately), acetate (saturated) and hydrochloride (1 per cent.). To the hydrochloride solution sodium bicarbonate was added till the solution was nearly neutral but not sufficient to precipitate the strychnine. Dilatation of the arteries results with all strychnine salts.

This reagent was tested for a possible bearing on the experiments of Düsser de Barenne on the local strychninization of the cortex. He mentions having used a 3 per cent. strychnine sulphate solution in some of his work. This statement must be a misprint for 3 per cent. strychnine hydrochloride, since the sulphate (according to Martindale and Westcott) is soluble only 1 in 62 of water and the acid sulphate 1 in 42.

It seems probable, however, that the slight amount of dilatation produced is of no significance in connection with his experiments.

VI.—Asphyxia.

The observations on asphyxia were carried out on both cats and rabbits, under ether in some cases and chloral in others. The results were the same with both anæsthetics.

To produce the asphyxia the trachea was ligated.

The arteries during the course of the asphyxia showed no active alterations, either contraction or dilatation. When the blood-pressure had become almost abolished there was a very slight diminution of the diameter of the large arteries, but the most noteworthy fact was the very small degree of variation to differences in internal pressure.

The veins, on the contrary, were seen to swell up and become more rounded in shape, and this swelling of the larger veins was communicated to the venous capillaries, large numbers of which came into prominence which had not been visible before in the superficial cortex. With the progress of the asphyxia the swelling became much less marked, but the capillaries still remained prominent. The blood-stream was first observed to slow in the veins, in which the pulsatile nature of the flow became more and more marked, until oscillatory movements and finally stasis supervened.

The flow in the arteries exhibited this same sequence of changes. Slow movements of the blood to and fro continued to be seen, most marked in the arteries, but present in the veins also, for at least twenty minutes after the tying of the trachea. The red corpuscles, as the stream slowed down, tended to group themselves into clumps with clear intervening spaces of plasma.

With the progress of asphyxia this segregation became very marked, till at the end of fifteen minutes (when slight movements of the blood to and fro were still taking place) long lengths of arteries and veins could be seen to be filled with plasma only, while short lengths showed a close packing together of the corpuscles.

VII.—Nerve Supply to the Cerebral Vessels.

The assumption is justifiable that, if present, the vasomotor nerve supply to the cerebral vessels is through the sympathetic system, the nerves of which presumably would pass through the stellate ganglion.

This assumption was tested by exposing the ganglion by the usual operation of resection of the second rib close to the vertebral column; the cardiac and inferior branches were cut. The cortex was examined microscopically while the ganglion was stimulated by a faradic current. Neither contraction nor dilatation was observed.

In a monkey the cervical sympathetic cord was stimulated but no effect was observed from this procedure. The rate of interruption of the primary was varied from fifteen to fifty per second, but this had no effect. The pupil dilated very actively, showing that the nerve trunk was being subjected to stimuli which were adequate for its fibres.

The stimulation of the vasomotor centre itself, together with the whole of floor of the fourth ventricle, was also tried. This centre was exposed by removing the skull covering the cerebellum with nibbling forceps. A small portion of the cerebellum was removed to expose the floor of the fourth ventricle, which was then thoroughly explored with a monopolar electrode manipulated by an assistant, but no place was found the stimulation of which affected the cerebral vessels.

On stimulation of the vagus centre the blood-stream in the veins was seen to cease and that in the arteries became quite visible, owing to the great slowing down, due to the inhibition of the heart. The calibre of the vessels was however not altered by this diminution in blood-pressure. This result moreover showed that the medulla was in an active condition, capable of reacting to stimuli.

The effects of a general rise of blood-pressure were minimized as far as possible by cutting the splanchnic nerve below the diaphragm.

VIII.—Experiments with the Convulsant Thujone.

Thujone, the active principle of absinthe, was used in these experiments. It was injected in a 50 per cent. solution in alcohol into the saphenous vein; the resulting fits were very violent and prolonged.

The cortex was observed in the usual way; in one experiment without, in another with a glass window inserted. This window was affixed after draining away a portion of the cerebrospinal fluid by puncture of the atlanto-occipital membrane with a needle attached to a syringe; this latter procedure enabled the skull defect to be kept relatively dry during the insertion of the window. This was affixed by means of dentists' oxyphosphate of copper cement, which sets in the presence of a slight amount of moisture.

In both experiments no contraction of the arteries was observed before the onset of the fits.

Macdonald and Cobb have described a preliminary blanching of the cortex. They expressly forbear from attributing it to arterial constriction. In the present observations no arterial constriction was at any time observed, though by means of blood-pressure records it could be shown that the vasomotor centre was vigorously stimulated.

The local application of thujone was also without action on the cerebral vessels.

The explanation of Macdonald and Cobb's observations would appear to be as follows: According to their tracings there is a simultaneous and marked fall of venous, arterial, and cerebrospinal fluid-pressures before their subsequent considerable rise. The onset of this fall is considerably before the commencement of the muscular convulsions. As they worked with an open skull there was a mechanical emptying of blood from the skull before the fits began owing to the pressure relations described. This probably accounts for the blanching they observed.

With the onset of the fits there ensued a great bulging of the brain into the trephine hole, and an exudation of fluid. The veins became rounded instead of presenting their somewhat flattened appearance, due to their great filling. The venous capillaries became more clearly defined, and many more were evident. The arteries were fully distended, but the picture presented was that of an intense venous hyperæmia, which continued so long as the fits endured.

From these observations it would seem impossible to associate any active participation of the cerebral-vessels in a thujone fit.

IX.—Inflammatory Phenomena.

The inflammatory phenomena presented by the cerebral vessels are in many respects those common to all regions, but their peculiarities throw a certain amount of light on a possible nervous control of the vessels, and there are present certain other phenomena interesting in themselves.

A good demonstration of thrombus formation can be obtained in the cerebral vessels. Usually in rabbits, at a variable time after the commencement of observation, small opaque perfectly white rounded bodies began to form in the veins, those of all sizes being involved in the process. These bodies adhered to the wall of the vein and visibly increased in size until they suddenly became detached and shot off into the blood-stream. The process was repeated many times until the growth was of sufficient size to block the vein; but complete blockage did not immediately ensue, for a slow tortuous stream could be observed for some time forcing its way through the white mass. Eventually complete stasis over a considerable area may occur, due to the blocking of the arteries and veins by these bodies.

The same process occurred in the arteries, but was much more difficult to observe owing to the great rapidity of the flow in them, but if for any reason this became retarded the process could be easily observed.

In cats such appearances rarely occurred spontaneously, even after very prolonged observation, or after the onset of considerable inflammation. If, however, a very acute inflammation were induced, e.g., by injecting just beneath the cortex a quantity of chloroform or any similar irritating agent, exactly the same process of "white body" formation occurred. The thrombi were formed also beneath the pia, in the cortex, and could be seen to come up out of the emergent veins.

By histological examination it was found that these "white bodies" consisted of an agglomeration of white corpuscles, mainly polymorph leucocytes, masses of blood platelets and a small amount of fibrin entangling a few red corpuscles; they were, in fact, early thrombi.

In the cat the effect of an extremely localized inflammatory agent was best studied by burning a small point with a hot glass rod. The application of chemicals to a local point is extremely difficult, if not impracticable, owing to the fact that the cerebrospinal fluid quickly or slowly, according to the nature of the irritant used, diffuses it over a wide and uncontrollable area. In the case of the localized burn however the disturbance of the circulation in its neighbourhood was strikingly absent.

The circulation in the vessels appeared to be the same at the end of two hours as when the injury was first inflicted, except in the case of the vessels actually injured or destroyed by the cauterization. It was thought that the continuation of observation beyond this point would introduce the complicating factor of an inflammation due to exposure to air.

If such an irritant as iodine was applied, or if the cortex was left exposed, the following sequence of changes was observed (the iodine dissolved in alcohol, in strength 4 per cent., was applied either by means of fine glass rods or by placing pieces of blotting-paper soaked in the solution on the cortex previously dried.) The first thing noted was a contraction of the arteries in the regions which the irritant reached but not elsewhere. In the course of ten to fifteen minutes this contraction gave place to a dilatation which endured for several hours. At the same time the circulation was seen to be rapid in the venous capillaries and in some of the veins.

A striking feature which manifested itself within one to two hours was a great increase in the number of venous capillaries visible in the most superficial layers of the cortex. They appeared to be very full of blood and were the first parts of the circulation to pass into a condition of stasis. In favourable places a concurrent great dilatation of the fine arteries and arterial capillaries could be seen. In view of the fact of the total lack of response of the venous capillaries to all other forms of stimuli the explanation would seem to be that the dilatation of the arterial ends of the capillaries influenced the venous ends passively.

With the progress of the inflammation typical slowing and then oscillating movements appeared, first in the capillaries and then in the veins and arteries, until the whole of the inflammatory area assumed a state of stasis. Before the onset of complete stasis, however, extravasation of small pin points of red blood corpuscles appeared around the capillaries, and these gradually increased in size till much of the deeper circulation was obscured from view. The corpuscles tended to spread along the courses of the larger vessels, especially the veins, being separated from them by a narrow clear space. The white corpuscles could not be distinguished against the cortical background. At the same time that these vessel changes were occurring an œdema developed which manifested itself as a swelling of the cortex through the trephine opening, and also by the fact that the superficial layers of the cortex became more transparent.

As so far described the cortical vessels offer no striking difference in their reactions in inflammation from vessels of other regions.

A noteworthy point, however, is the strict limitation of the phenomena. This was best exemplified in a preparation in which inflammation had been induced by exposure to air, but it was also seen when other methods were used. If a trephine hole were made close alongside the original hole and the two carefully opened into one another by bone

clippers, it was seen that there was a comparatively sharp edge separating the two areas, the circulation in the freshly exposed portion being normal.

To the naked eye there was not a very great contrast in colour between the two portions, but if the animal were killed and the brain extracted the inflamed portion stood out as a red, sharply marked circle, there being no gradation into the surrounding normal cortex.

A histological examination of the cortex displayed a plentiful diapedesis of white cells, polymorph leucocytes being prominent though many mononuclear cells were also present. A noteworthy fact was that the inflammatory products were almost totally to be observed in the pia itself and only the most superficial layer of the cortex ever showed involvement. It was extremely rare to find a polymorph cell within the cerebral substance. However, this point deserves further investigation as the depth to which the irritant penetrates is not known.

X.—Discussion of Results.

Though the method of direct observation of the cortex is anything but new, the use of the microscope is only once recorded in the literature.

The results of the first microscopical observations were published as long ago as 1866 by Schultz. He does not describe his microscope or the powers of magnification; he used "good illumination."

He noticed, and the foregoing observations almost entirely confirm his statements, the pulsations in the vessels, the respiratory alterations in the size of the veins and contraction of the vessels to electrical stimuli. His experiments also failed to find any action from cutting and stimulating the cervical sympathetic.

Several observers have used simple inspection of the cortex. Other methods of observation consist of various perfusion and blood-pressure measurements. The discordance of these results is remarkable, one set of experimenters stating that their findings are in favour of the presence of vasomotor control of the cerebral circulation, another set with similar methods denying that any evidence is forthcoming in support of this thesis.

It would seem possible that this discrepancy is due to the disregard of one or more of the numerous known factors which can upset the cranial pressure arrangements, or to some intrinsic defects of the methods.

The utilization of the method of direct observation has shown that

the cerebral vessels react, as do other vessels, to mechanical and electrical stimuli. The arterial ends of the capillaries have also been shown to possess the property of contractility.

But it is difficult to conceive of conditions in life in which either of these two agents, or that of the chemicals producing reactions, would cause these contractions.

The use of cold applications to the head have been used therapeutically to assist in the arrest of intracranial hæmorrhage. That cold does penetrate as far as the cortex after the application of an ice-bag has been shown to be the case by Sherrington and Leyton, who worked on the chimpanzee. Certainly contraction does occur with cold but it is usually not great. It would seem that the use of cold clinically may possibly do some good, but its constrictive effects are probably quite small. If one could apply heat at about 45° C. this would be perhaps more effective, but it would be difficult of application.

It was thought that the localization of the contraction to the point stimulated indicated that the arteries were not innervated, but the mesenteric vessels which certainly have a vasomotor supply react in an identical way.

Riegel and Jolly have also recorded their observation of the fact that the cerebral arteries contract to mechanical stimuli; Nothnagel, and Riegel and Jolly noticed contraction to cold applications.

No observations on the effects of warmth have been recorded in the literature consulted.

The most important of the chemical substances tested was adrenalin. The results previously recorded are remarkably discordant. By the use of various methods the following authors arrive at the conclusion that constriction occurs: Biedl and Reiner, Wiggers, Roberts, Mellanby and Huggett, and von Cyon. Huggett and Mellanby have of late withdrawn their statement that adrenalin causes constriction of the vessels supplying the respiratory centre. Dilatation is stated to occur by Dixon and Halliburton, Spina, Cow, and no action was recorded by Hill and Macleod.

In the present observations constriction never occurred under any circumstances, but occasionally a slight dilatation was noticed. This fact necessitates a reconsideration of the views of Roberts on the causation of adrenalin apnœa which he claims is due to anæmia of the respiratory centre. For such an anæmia, giving apnœa, a very considerable contraction of the vessels would presumably be necessary. By direct observation, however, the vessels on the anterior of the medulla and

the floor of the fourth ventricle were found not to contract to adrenalin.

Of course the vessels actually supplying the nervous tissue of the respiratory centre could not be seen, but it would seem unreasonable to attribute a constricting action to such a limited portion of the intracranial circulation, when the whole of the visible portion is quite unresponsive.

The observation, with pituitrin, with which no contraction was obtained, is difficult to understand on the view that pituitrin stimulates plain muscle fibre, as the vessels possess such, which is capable of reacting vigorously to other stimuli.

The previous results recorded with this substance are also discordant Roberts states that it causes contraction of the vessels supplying the respiratory centre, Dixon and Halliburton that it causes first a contraction and then a dilatation, both slight; and Cow that there is no action.

All observers are agreed that amyl nitrite causes a dilatation of the arteries (Biedl and Reiner, Cow, Gaertner and Wagner) and that barium chloride causes contraction (Dixon and Halliburton, Wiggers, Cow and Roberts).

The question of a vasomotor control of the cerebral vessels.—The presence of nerves along the cerebral vessels has been known for a considerable time, but as yet no satisfactory evidence has been forthcoming as to their function. Obersteiner, Morison, Gulland, Hunter, and Huber, using a variety of histological methods, have described these structures, but Rohnstein and Robertson deny that they are of nervous character.

The results here recorded, from the stimulation of the stellate ganglion and the vasomotor centre itself, have produced no evidence for any vasomotor function for these nerves.

Indirect evidence for the absence of a vasomotor control can also be given. The experiments on the production of asphyxia failed to show any active alteration in the calibre of the cerebral vessels, though it is known that in such a condition the vasomotor centre is vigorously stimulated.

The experiments on thujone likewise produced negative evidence. Here again there is a vigorous stimulation of the vasomotor centre, but no action could be observed on the cerebral vessels.

The strict localization of inflammation to the locus of action of the harmful agent would again tend to show that the cerebral vessels are free from those reactions occurring in other parts of the body which are dependent on reflexes, whether of the central or axon type.

All other arteries which have been found to be under the control of vasomotor nerves react to adrenalin by contraction, but the cerebral vessels fail to do this.

However, Krogh states that the capillaries of the frog's web, though under sympathetic nerve control, do not react to adrenalin, but that the arteries do. It is just possible, disregarding the other negative evidence, to conceive of the cerebral arteries acting in an analogous fashion to that of the capillaries of the frog's web. All the evidence given is, therefore, emphatically against the recognition of any effective intracranial vasomotor control, in spite of the fact that the vessels are capable, with appropriate methods of stimulation, of entering into strong contraction.

The possibility remains that under certain pathological conditions, e.g., arterio-sclerosis, a spasm of some arteries may occur. The mechanism by which such could occur is obscure, but possibly some abnormal metabolic product, which in a normal condition of the arteries is without effect, in the damaged state may produce contractions. However, that such a transient spasm does occur is rendered probable by the comparatively rare but well recognized fact that transient paralyses do occur, similar in all respects to those produced by hæmorrhage, from which the patient makes a remarkably rapid and complete recovery.

XI.—Summary.

(1) A microscopic method for the examination of the cerebral cortex is described.

(2) The cerebral arteries react to mechanical, thermal, electrical, and chemical stimuli by contraction and dilatation.

The arterial ends of the capillaries also show this capacity to contract.

(3) No evidence is forthcoming for the presence of any nervous control over the calibre of the cerebral vessels.

(4) Thrombus formation and the early stages of meningitis are described.

The inflammatory changes observed in regard to the cortical vessels are essentially the same as those occurring in a region supplied with vasomotor nerves.

My sincere thanks are due to Professor Sherrington for constant encouragement and much helpful advice, and to Mr. H. M. Carleton for considerable help with the histology involved. I have gratefully to acknowledge the kindness of Professor Krogh, who demonstrated his methods of investigating capillary function.

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ASTEREOGNOSIS: ITS CAUSES AND MECHANISM.

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In a previous work, published in 1922 [1], I had occasion to draw attention to the relations between the alterations of tactile discrimination revealed by Weber's method and astereognosis.

I then gave particular attention to cases of pure astereognosis, that is to say, to cases in which there were no alterations of elementary sensibility or affection of the motor system. In such cases it is constantly found that whilst the faculty of perceiving and localizing accurately simple contacts and thermal and painful stimuli, as well as the slightest movement of the fingers and of their joints, is preserved, serious alteration can be always detected by Weber's method, and there is always some loss of the sense of position. We shall see later the reasons why it may be assumed that the latter defect has no important influence on astereognosis. It is, however, always present. It is worth noting that when patients who retain delicate sensibility of movement are asked to make small excursions with their fingers they succeed always in recognizing the position into which each finger is brought; they are therefore able to reproduce the corresponding attitude with the other hand when their eyes are shut. It is only when the hand is absolutely at rest that it is possible to determine to what degree deep sensibility is lacking; this defect may escape the casual observer, who may also fail to detect the loss of tactile discrimination if he omits to make use of Weber's compass.

In short, as already noted by Dejerine, there are no cases of pure astereognosis, for there are always concomitant and more elementary alterations of muscular and tactile sensibility.

Numerous observations permit me to state:—

(1) In cases of astereognosis there is always a considerable diminution of tactile discrimination as revealed by Weber's method, as well as of the sense of position. All other forms of sensibility, on the contrary, may be normal.

(2) Whenever such alterations exist there is always astereognosis,

which varies in severity with them; this holds true in diseases of both the central and peripheral nervous systems.

(3) When astereognosis is limited to one portion of the hand, these changes in tactile discrimination and the sense of position are also confined to this part.

(4) As astereognosis recovers these defects disappear *pari passu*.

These conclusions practically agree with those arrived at by other observers, as Dejerine, Christiansen, Knut Malling, Hoffmann, Krestnikoff, Spearman, Gans and others. It is important to discuss how they may influence our ideas about physiology and pathology of the astereognosis. For greater clearness I shall limit myself to some fundamental points:—

(1) *Astereognosis is not a form of agnosia, nor does it result from a loss of special sensorial images.*

To explain the inner mechanism of astereognosis reference is usually made to the same principles which have served as a basis to the various doctrines of aphasia. By some the existence of special stereognostic images have been assumed, which would play the same part in the recognition of the geometrical properties of bodies by touch as was formerly attributed to verbal images in recognizing graphic and phonetic symbols. Others, on the contrary, have regarded astereognosis as a form of agnosia, as a result of which the tactile sensations corresponding to various geometric forms cannot be identified. It is, however, possible to make an experiment on the special type of patients I have examined, which, by itself, seems sufficient to disprove these hypotheses.

Those stereoagnostics who preserve the perception of simple tactile stimuli are able to recognize perfectly and distinguish when their eyes are closed any geometric figure that may be traced on their hands by a pencil, as, for instance, a circle, a triangle, a cross, a letter of the alphabet, a number, or even more complex forms, according to the power of attention, the intelligence and the culture of the patient. Although they may not succeed in recognizing by its form a small ring placed flat on the palm of the hand, they recognize at once a small circle of similar dimensions traced with a point on the same area of skin. This depends upon the different manner the skin is stimulated; in the first instance there are many simultaneous tactile sensations which the patient, owing to the defective faculty of discrimination, as can be determined by Weber's test, is unable properly to distinguish and detect; in the second there is a succession of simple tactile stimuli each of which can be distinctly perceived and well localized on the

surface of the skin, so that the figure formed by all of them stands out clear and defined. This test, however, does not succeed when the perception of simple contacts is also defective.

This experiment shows that those who suffer with astereognosis can perceive and recognize by the sense of touch geometric figures, provided they are presented to them in a proper way and having regard to the extent of their sensorial trouble. To speak, therefore, of "asymbolia," and of "loss of specific sensorial images," is inaccurate.

These experiments are very similar to those so ingeniously carried out by Head in his investigations of aphasia.

As a matter of fact, a form of tactile agnosis exists which, as it leads to a serious difficulty in recognizing objects, may simulate astereognosis, but it is something altogether different from it. This form has been recently described by P. Marie, H. Bouttier and L. van Bogaert [2] in a case of a left prefrontal tumour. The patient recognized perfectly the fundamental characteristics of volume, quality, solidity and area of objects, and he could also analyse and describe their form, but he did not succeed in synthesizing all these data so as to obtain a notion of the object. Obviously in this case there was a particular type of disorder of higher functions. I had once the opportunity of making similar observations in the case of a woman who, after an attack of eclampsia, had a right hemiplegia. During recovery there was astereognosis in the right hand, though the elementary forms of sensation to the various tests, including Weber's, were normal. This patient, however, recognized the various spatial qualities of the object she handled, but it was only when the observations which she herself had made were enumerated and summed up for her, and her attention was thus stimulated, that she succeeded in recognizing the object itself. From that moment recognition was assured in all successive tests. A similar condition was found on investigating her disturbances of speaking and her apraxia.

(2) *Astereognosis has no connection with disturbances of deep sensibility.*

In addition to disturbances of tactile discrimination as revealed by Weber's tests, I have always found in my patients marked alterations in deep sensibility, usually limited to the sense of position. I cannot offer a definite explanation of this, but several circumstances induce me to believe that these disturbances of deep sensibility are of no fundamental importance so far as astereognosis is concerned.

In the first place, I have found that patients in whom the sense of

movement was preserved may, by means of small movements of the different joints of the fingers, recognize without the help of sight the attitude of the whole hand, and yet in spite of repeated handling of objects they cannot even approximately detect their form.

Secondly, in a case which I report here, the sense of position was defective and slight alterations in discrimination could be detected by Weber's compasses, yet the patient, although he made some mistake in estimating the dimensions of objects, recognized the form of all test-objects immediately.

D.L., aged 45, a syphilitic patient, had recently had two Jacksonian epileptiform attacks affecting the upper left limb. There was no appreciable disturbance of mobility.

Superficial sensibility was normal in all its forms. Weber's tests revealed a slight difference between the right hand and the left hand, but at the finger-tips the difference was scarcely 1 mm.

Deep sensibility.—The appreciation of vibration persisted and the sense of movement was intact. The sense of position was very defective in the whole right upper limb, and especially in its distal portions. Similar changes were noted in the right lower limb, but they were more difficult to demonstrate.

Stereognosis.—The patient recognized and distinguished well by touch even the smallest objects, but his perception of dimensions, and especially of thickness, was affected. A pin appeared to him almost as large as a nail, a small 5-cents coin, held by the flat surfaces between the thumb and the index finger, seemed smaller and thicker. These errors did not prevent the recognition of the form of objects, and consequently there was no astereognosis. The incorrect estimate of thickness was undoubtedly to be attributed to the deficient perception of the postural relations between the finger-tips; while the slight error in estimating the extension of surface was probably due to the slight alterations revealed by Weber's test.

(3) *Astereognosis is a result of that peculiar deficiency of tactile discrimination which is revealed and can be measured by Weber's test.*

The clinical facts recorded above undoubtedly constitute strong presumptive evidence in favour of this hypothesis, but they do not explain the causes thereof. To understand them it is necessary to consider all the symptoms which characterize astereognosis. Above all we must remember that the faulty perception of form is not the only trouble. There are also serious disturbances in the more elementary perceptions which are the essential basis of the development of stereognosis.

It is easy to ascertain that while a healthy person feels and recognizes an angle or a surface and the presence of any object by simply touching it with the tip of his fingers, the stereoagnostic on the contrary, although he may touch and grasp an object, is not aware of its presence in his hand, especially if it is of light weight and of a small volume, and although he touches and moves his fingers repeatedly over a surface he has no clear perception of the existence of the surface or of the angles he encounters. The stereoagnostic has merely sensations of a subjective character; they are sensations of efforts and movement. Thermal and painful sensations and tactile impressions (when elementary tactile sensibility is fully preserved) are referred to an external object only by induction; the real perception of a material object is lacking absolutely.

These two facts are necessarily connected. As far as touch is concerned practically only solid bodies are considered as material objects. They are recognized as such only owing to the fact that they are limited by surfaces apt to impress the sense of touch. It happens, consequently, that when the faculty of feeling a surface is lacking it is also impossible to detect the existence of a solid body and to recognize its form.

Why cannot these patients feel a surface? They can perceive each single contact and localize it accurately on their skin; they can also distinguish and localize one by one the successive contacts produced by a point moved over their hands. Each sensation is related to one point of the cutaneous surface only, but the sum of these sensations, succeeding each other in time and properly arranged in space, forms the basis of the perception of lines and linear figures.

A surface, on the contrary, produces manifold simultaneous tactile impressions, and we are enabled to perceive it owing to our normal faculty of simultaneously perceiving numerous contacts differently localized within the cutaneous area coming in contact with that surface.

Patients with astereognosis have lost this faculty; in fact by Weber's tests it is found that in those parts of the hand particularly adapted to touch they do not distinguish the two points of a compass unless they are wide apart. It generally happens that the distance between the two points is greater than the area of skin coming in touch with the object; frequently the two points fall on different phalanges of one finger. Even then, however, only one of the contacts, that on the proximal phalanx, is properly recognized and localized. The localization of the other is generally defective. If there is a lesser distance between

the points of the compass the patient may have the impression of a single contact only, which is either referred to an intervening point or is not at all accurately localized; as a matter of fact the clear perception of a double contact is lacking in almost every instance.

Normally, those parts where the discrimination of two points close together is more acute, as at the finger tips, are also the parts which perceive and recognize accurately small solid bodies with limited surfaces, and here stereognosis is also most accurate.

There are pathological cases where stereognostic perception is very feeble and difficult but not wholly abolished. In these cases by using Weber's compass we obtain on the tips of the fingers and on the hand values scarcely equal to those normal for other parts of the body where stereognosis is usually less perfect. In short there is a constant relation between the faculty of stereognosis and the ability to perceive and discriminate many simultaneous contact points close to each other. The investigation of clinical cases further shows that this form of sensation may be altered by lesions of the cerebral cortex as well as by injuries to peripheral nerves, so astereognosis may be caused by disease of the cortex of the brain (parietal lobe) as well as by lesions of the peripheral sensory nervous system.

In the foregoing notes I hinted at some analogies existing between the disturbance of stereognosis and those of language. I wish to draw attention to a case which may be of some interest, especially as it may lead us back to the idea expressed by Head in his work on aphasia and allow us to view these different functional disturbances in the same light. The essential changes appear in fact to belong to the one type, although related to different functions according to the portion of the cortex which is involved, so that one is forced to assume a special physiological mechanism peculiar to certain cerebral areas and connected with various functions; when this mechanism is injured the symptoms that result are always of a complex character.

The patient had complained for over a year of disturbances of sensation in his right hand, of a slow deterioration in speaking and reading, and of a difficulty in performing the simplest mathematical operations, although his intelligence and memory remained unimpaired. Tests revealed astereognosis in the right hand only, accompanied by defective tactile discrimination as revealed by Weber's test, and loss of the sense of position, as well as aphasia of an amnestic type and acalcolia; the more elementary forms of sensation were unaffected. The patient was under observation for a year, and as his trouble showed no change and as no special symptoms developed, the diagnosis made was atrophy of the

parietal cortex of the Pick type. I still consider this diagnosis as probable.

It is interesting to consider the special features of the aphasia shown by this patient. He spoke slowly, his thought was clear and his syntax correct, but he stopped in speaking as though failing to find his words, and in order to express himself he resorted to round-about phrases. On investigation of his symptoms it was found that in spontaneous speech and in naming objects he did not succeed in enunciating the words formed of three or more syllables, while he used with ease words of two syllables. A similar condition was noticed in mental reading and in writing to dictation. It is, therefore, clear that his defect was not due to lack of intelligence or of the representation of vocal symbols, nor to any motor disorder of speech, but only to an incapacity to formulate mentally words of complex structure.

In this case it was easy to perceive a close analogy between this affection of speech and his disturbances of sensation. The patient failed to detect by his hand a series of tactile impressions, and similarly he was unable to grasp and formulate at once a series of phonetic perceptions and representations forming words, when these constitutive elements exceeded a certain number. Here we have an indication of a special physiological mechanism which is perhaps an innate function of certain parts of the brain. It may be also possible to attribute to a disorder of this same physiological mechanism the difficulty which the patient experienced in reckoning.

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RESPIRATORY DISORDERS IN EPIDEMIC ENCEPHALITIS.

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I.—Historical.

Epidemic encephalitis is now regarded as one of the most disabling diseases of the nervous system. Its late effects have been studied and described with great care and an extensive literature has arisen. Amongst the sequelæ, disorders of the respiratory mechanism have been regarded as rare after-effects. A study of the most recent monographs (Hall [29], Lévy [34]) has shown, however, that respiratory disabilities take quite a large and important share in the general post-encephalitic picture.

The more frequent occurrence of these disabilities has received confirmation from our own recent experience, as we have observed the existence of minor respiratory symptoms to be not uncommon if looked for in association with Parkinsonism and other well-recognized effects of this disease.

(1) *Respiratory Symptoms in the Acute Stage.*

The first descriptions of respiratory abnormalities accompanying an acute attack of epidemic encephalitis appeared in 1920. By far the most common disorder is tachypnœa, in which the respiratory rate may be as high as 80 or even 100 per minute. There is usually no accompanying increase of heart rate, and cyanosis or thoracic distress is rarely present. Such cases have been recorded by Achard [2], Roubier and Richard [54], Baumel, Sentis and Milhaud [8]. Happ and Mason met with hyperpnœa in 6 out of 81 cases and Dunn [23] in 3 out 115 cases. In some instances, the hyperpnœa comes on only during sleep (Mendicini) [43]; in a case recorded by Marinesco [41] the patient had a polypnœa which exactly synchronized with myoclonic contraction of the left biceps.

Our seventh case exemplifies the occurrence of tachypnœa during the acute phase; in this patient respirations were short and noisy and the

rate was increased—at times up to 64 per minute. Other forms of respiratory disorder are met with less commonly during the acute phase; thus Blouquier and Claret [12] record a fatal case of the myoclonic variety of encephalitis in which there was difficulty in inspiration, paroxysmal in type, causing cyanosis and pauses of apnœa lasting twenty seconds. Goldflam [27] speaks of Cheyne-Stokes respiration, polyuria and respiratory tics as phenomena occurring in the acute phase of epidemic encephalitis. Boyd [14] met with rapid breathing in many cases during the 1923 epidemic in Winnipeg.

In other cases again the acute period of encephalitis is free from disorder of respiration, but the early weeks of convalescence become complicated by polypnœa. Thus Aronson [4] writes of a case of hyperpnœa occurring in a boy of eight years during convalescence from encephalitis; the rapid breathing was transitory in nature and cleared up after seven months. Barker and Sprunt [7] recorded a case of encephalitis lethargica, which five weeks after the acute phase developed hyperpnœa and tetany.

(2) *Respiratory Disorders as Late Effects.*

Amongst the sequelæ of encephalitis, disorders of respiration constitute a variety which only lately has received special attention. The earlier descriptions of such cases were made chiefly by French and American writers, and were regarded at first as rare or unusual manifestations, frequently labelled "hysterical" in nature. Gradually, however, it became realized that disorders of respiration form well-defined and important sequelæ which may constitute the sole after result, or may on the other hand accompany Parkinsonism, mental aberration, sleep disturbance or any other well-recognized sequel.

One of the earliest writers to record such cases was Bériel [9], who reported three cases of post-encephalitic Parkinsonism accompanied by polypnœa (60-80 per minute) with shallow respirations. Babinski and Charpentier [5] and [6] showed two patients: one, a female, aged 27, who had symptomatic paralysis agitans following encephalitis lethargica. In this patient respiration was rapid, noisy and nasal in character, as though trying to dislodge a foreign body from the nose; these effects were followed by periods of apnœa terminating in slow, deep breathing. This disorder of respiration came on only when in bed at night, and was to a limited degree under voluntary control. The second case was a boy, aged 18, who in addition to post-encephalitic Parkinsonism had irregular, rapid and noisy respiration occurring throughout night and day. There

was also a well defined inversion of the sleep rhythm. At the same meeting Souques [58] mentioned a case of his own in which a little girl, as a result of encephalitis lethargica, developed noisy expiratory breathing which was described by her father as resembling a dog barking. Cases have been described by Sicard and Paraf of respiratory tics, comprising yawning, hiccough, stretching, sobbing and uncontrollable laughter. Hass mentioned a child, aged 2, who showed paroxysms of forced breathing followed by spells of breath-holding, cyanosis and unconsciousness. Harvey Parker [48] has described a number of cases observed in the Mayo Clinic suffering from various respiratory dysrhythmias: such were paroxysms of breath-holding—in some instances coming on at night only. The apnœic spells were accompanied by many peculiar attitudes or gestures, such as standing up and bending the trunk backwards and forwards, grimacing, choreo-athetotic movements of the limbs or running of the fingers through the hair. Other respiratory disorders were noisy and grunting expirations, and in one case difficulty in breathing which came on only when the patient was erect. In no case was the respiratory disorder the sole after-effect, Parkinsonism, psychical or sleep disturbances being also present.

Laignel-Lavastine and Maingot refer to cases in which the respiration was interrupted by apnœic pauses. In other instances there was noted on the fluoroscopic screen an asynchrony between the movements of the two halves of the diaphragm. Leroy and Dupouy [33] recorded a patient who showed, in addition to dyspnœic paroxysms, polyuria and Cheyne-Stokes respiration. In 1922, Pierre Marie and Mlle. Lévy [39] and [40], in addition to quoting seven cases of their own, reviewed all the hitherto recorded instances of respiratory sequelæ of encephalitis, placing them into three categories: (1) true respiratory disorders (polypnœa, bradypnœa, apnœa and periodic respiration); (2) spasmodic cough; and (3) respiratory tics and abnormal naso-laryngeal sensations. Kennedy, David and Hyslop [32] recorded two cases of paroxysmal dyspnœa associated with polydipsia and polyuria.

Vincent and Bernard [61] drew attention to a peculiar disorder in the thoracico-abdominal mechansm of breathing which they had observed in several cases of post-encephalitic paralysis agitans. In some of their patients the expansion of the chest was reduced to 1 cm. only, the lower half of the thorax being held in a position of full inspiration and immobile. In other cases no movement of the diaphragm occurred owing either to paralysis of that structure, or to its fixation in an attitude of immobile spasm.

Naville [45] records the case of a woman, aged 30, three years convalescent from encephalitis lethargica, exhibiting polypnœa and bradykinesia. He also referred to a child who had shown Cheyne-Stokes respiration. Roch [51] recorded a case of symptomatic paralysis agitans, with paroxysmal dyspnœa, each attack lasting a minute or so and accompanied by cyanosis and tachycardia. A recrudescence of the original infection had the effect of aggravating the respiratory attacks both in number and intensity. Another case of post-encephalitis with respiratory, "bradytrophic" and psychical sequelæ has been reported by Chiray and Lafourcade [20].

Urechia and Mihalescu [60], after reviewing the literature of the subject, also reported a case of their own: the patient, a girl of 9, was affected with paroxysms of inspiratory apnœa, during the height of which chorea-athetotic movements of the fingers took place.

Miss Anderson [3], in reviewing forty cases of children recovered from encephalitis lethargica, found "hysterical" hyperpnœic breathing present in a large proportion: all children with severe psychical disturbances gave evidence in addition of respiratory disorders; hyperpnœa was the commonest manifestation, but in many there was noisy and rapid respiration occurring either continuously or in paroxysms; one child was stated by her parents to "pant like a dog." These "habit peculiarities" were to a certain extent under voluntary control. One child in her series, aged 3, had spells of breath-holding of such violence that the muscles of her chest and back hypertrophied.

Barker and Sprunt [7] have placed on record an interesting case in which a young man of 18, five weeks convalescent from encephalitis lethargica, developed paroxysmal attacks of deep, laboured respiration "like asthma." Later peculiar mental lapses appeared and on admission to hospital the patient developed a well-marked attack of tetany.

In an interesting paper Etienne Bernard [10] in 1923 brought the recorded cases of respiratory disorders up to date. Bernard classifies the phenomena in eight groups: (1) disorders of thoracic expansion; (2) tachypnœa and bradypnœa; (3) respiratory pauses; (4) dyspnœa with vasomotor disturbances; (5) inversions of the respiratory formula or rhythm; (6) sighs; (7) respiratory disorders associated with myoclonus; and (8) respiratory "tics" and spasmodic cough.

Pardee [47] recorded five cases of paroxysmal respiratory dysrhythmias; his patients had momentary feelings of dizziness and then felt compelled to take a deep breath "as though something were compressing the lower chest and interfering with adequate depth of breathing."

Respiration became deeper, and expiration prolonged and frequently grunting. The hands were clenched and unclenched and the body became hypertonic. These paroxysms were partly under voluntary control; they were aggravated by emotional stimuli; the usual time for their appearance was towards nightfall. Cameron [17] has recorded a case of tachypnœa alternating with apnœa in which the child became cyanosed.

The first experimental work on this subject was published by Rosenow [52], who collected streptococci from the tonsils or naso-pharynx of the seven cases of respiratory disorders described by Parker at the Mayo Clinic. Suspensions of these cocci were injected into eighty-three rabbits with the production of marked hyperpnœa in sixty-five. Histological examination showed sharply localized œdema and pial infiltration on the ventral aspect of the upper pole of the medulla.

At the annual meeting of the British Medical Association in 1923, further cases of respiratory disorder were quoted. Thus Farquhar Buzzard [16] mentioned a case of paroxysmal dyspnœa in a young subject with a Parkinsonian syndrome; Hinds Howell [31] referred to three cases, one of hyperpnœa, one of dysrhythmia resembling Cheyne-Stokes respiration, and the third of spontaneous yawning; Macbride [37] referred to a case of torticollis following encephalitis, and accompanied by peculiar deep nasal inspirations.

Abrahamson [1] showed a case of myoclonic post-encephalitis in a boy, aged 4, who also presented psychical changes, insomnia and breath-holding spells. Another patient of his had paroxysmal deep inspiration, involuntary yawning, spontaneous movements of one leg and psychical disturbances.

Capgras and Reboul-Lachaux [19] also reported a case of paroxysmal polypnœa which, together with psychical aberrations, appeared as sequelæ of an encephalitic attack two and a half years previously. Roubinovitch, Baruk and Bariety [55] showed a case of a lad presenting mental symptoms after encephalitis, together with Parkinsonism and polypnœa, alternating with short apnœic spells.

In 1924, a further case of paroxysmal tachypnœa was recorded in Norway by Motzfeldt [44].

Hall [29], in his recent book on encephalitis, mentions various respiratory disorders and refers to three very interesting cases of his own; one was a patient who developed a respiratory tetany; another had sniffing inspiration which synchronized with jerkings of his arms; a third patient exhibited post-encephalitic adiposity, in addition to a spasmodic cough which had persisted for three years.

In a recent paper van Bogaerts [13] has recorded a case of tachypnœa associated with Parkinsonism, hepatic derangement and rapid pulse. The respiratory rate at first became increased only upon excitement; later it appeared as a post-prandial symptom, and finally as a constant feature. The tachypnœa was most marked when the patient stood up and diminished when in the supine position.

II.—Clinical Manifestations.

For descriptive purposes the respiratory disorders following epidemic encephalitis may be classified as follows :—

(1) *Disorders of the respiratory rate* (tachypnœa and bradypnœa).

(2) *Dysrhythmias, or disorders of the respiratory rhythm* (Cheyne-Stokes breathing, breath-holding spells, sighs, forced or noisy expiration, inversion of the inspiration-expiration ratio).

(3) *Respiratory "tics."*—(Yawning, hiccough, spasmodic cough, sniffing.)

It must be realized, however, that any combination of the above types may co-exist with or without the other sequelæ of encephalitis.

Before proceeding to a description of respiratory manifestations it is advisable to define the terms we propose to use.

Breathing which is faster than normal we shall speak of as "tachypnœa." The word "bradypnœa" we shall apply to slow respirations. Respiratory movements which are shallower than normal may be named "hypopnœa." The term "hyperpnœa" should strictly speaking be limited to those of abnormal depth. It may be pointed out here that tachypnœa is, as a rule, accompanied by some degree of compensatory hypopnœa. In this article we propose to discard the word "polypnœa" altogether.

(1) *Disorders of the Respiratory Rate.*

Tachypnœa constitutes one of the commonest of the respiratory manifestations. The increased respiration rate may be either continuous, in which case it bears no relationship to the output of work, or paroxysmal. The patient usually suffers no inconvenience and cyanosis is rare; in the majority of cases there is no accompanying tachycardia. The tachypnœa may occur during sleep only, or during both sleeping and waking states. On the other hand the respiration rate may fall during sleep or even when the patient is recumbent. Physical examination of the chest usually gives negative results, but in some cases, particularly in the presence of the Parkinsonian syndrome, there may

be a relative immobility of part of the thorax or of the diaphragm. The amplitude of each expiration is usually shallower than normal and may be saccadé or jerky in character.

Paroxysmal tachypnœa may arise in attacks occurring three to four times daily or several times in the course of an hour. It is sometimes observed that the paroxysms tend to come on towards nightfall, each one lasting anything from a minute to several hours. The patient is usually conscious of the increased respiration rate and is able voluntarily to control it for a short time. When questioned as to why he breathes more rapidly no very clear reply is given, but complaint may be made of a sensation of thoracic constriction or pulsation. Farquhar Buzzard [15] has pointed out that in many cases of post-encephalitis acts which are normally automatic in nature (swallowing, speaking, breathing, &c.) become purely voluntary actions. This statement is true for certain of these paroxysmal tachypnœas. The intensity and frequency of the attacks are increased by emotional stimuli, and conversely become less marked when attention is distracted. Frequently the act of deglutition temporarily inhibits the tachypnœa.

Of the complications of tachypnœa, tetany is the most important, and occurs in those cases in which the usual compensatory hypopnœa is replaced by respirations of full amplitude. The experiments of Collip and Backus [21], Grant and Goldman [26], Rosett [53] and many others have demonstrated that tetany is a physiological accompaniment of "over ventilation of the lungs" due to forced respiration, the causative mechanism arising through the altered H'/OH' balance. Vasomotor disturbances may also appear in the course of the tachypnœa, giving rise to lowered arterial tension and cyanosis of the extremities.

Children in particular are liable to display tachypnœa. This manifestation may arise during the acute phase, during convalescence, or as a remote sequel. When arising as a late result of encephalitis it is rare not to find some other abnormality, physical or psychical. Reference has been made to the association of tachypnœa with synchronous myoclonic contractions of the biceps muscle.

Bradypnœa, a much rarer phenomenon, may be continuous or paroxysmal. The respiration rate may fall to as low as six per minute, and pressure on the eyeballs sometimes reduces it yet further. The amplitude of each respiration is usually increased, and expiration tends to become prolonged and noisy.

(2) *Dysrhythmias, or Disorders of the Respiratory Rhythm.*

Sighs: This is one of the commonest manifestations. The patient in the course of normal breathing may suddenly give a deep sigh, which is followed by a short period of compensatory expiratory apnœa. These sighs may occur only during sleep, or, on the other hand, may come on after some slight exertion. In certain instances the patient at the same time may exhibit a tic-like grimace or movement, such as opening of the mouth or shrugging the shoulders. Occasionally the expiratory component is broken or "cogwheel" in character. At times a regular periodicity may be detected in the order of their appearance, each sign occurring after a definite number of respirations.

Apnœic pauses: Intervals in which no breathing occurs may take place as a result of sighing inspiration, during a spell of breath-holding, or spontaneously in the course of normal respiration. These pauses are particularly prone to arise during sleep. The resumption of respiration, unlike what is seen in Cheyne-Stokes breathing, is not "crescendo."

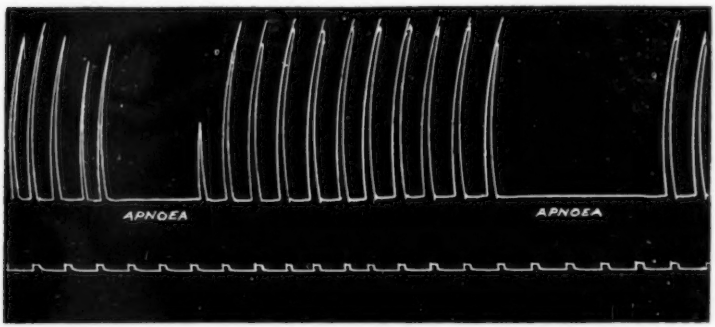

FIG 1.—Showing apnœic pauses of varying lengths interrupting respiration.

Inversion of the $\frac{inspiration}{expiration}$ *formula.*—In the normal waking state inspiration is shorter than expiration with the proportion of 5:8; during sleep the converse is true. In certain post-encephalitic patients the normal ratio is reversed so that the respiration during the waking state resembles that of normal sleep.

Cheyne-Stokes respiration.—This is a rare manifestation; Pierre Marie affirming that he has never seen a genuine case. Goldflam, Leroy and Dupouy, and Naville have, however, recorded cases of

abnormal breathing conforming to this type; tachypnœa constituted a marked symptom in their patients.

Bigeminal and trigeminal respiration.—In certain cases, a graphic record of the respiration reveals a regular arhythmia in the amplitude of each effort; for example, breaths may be alternately deep and shallow (*bigeminal or alternating respiration*); or a deep breath may be succeeded by two of smaller amplitude (*trigeminal respiration*). These abnormal types of breathing are frequently associated with the occurrence of sighs or apnœic pauses.

Breath-holding spells.—This subclass includes a great variety of interesting manifestations which differ from the simple apnœic pauses in that the breath is held in almost full inspiration. It is into this class that one must place the first and third cases recorded by us.

The paroxysms occur at irregular intervals and may or may not be interposed with periods of normal breathing. They tend to come on especially towards nightfall and in some cases (as in our third case) may be present only during sleep. In other instances (as in our first case) the paroxysms occur during the waking state only. The attacks, like those of simple tachypnœa, are to a limited extent under the patient's control and may be temporarily inhibited by voluntary effort, by deglutition or when attention is forcefully distracted. Similarly, the attacks increase in number and frequency when the patient is under emotional stress or is the object of marked attention.

The paroxysms are ushered in by a series of deep, forced inspiratory efforts with noisy expirations; the patient's subjective sensations at this stage frequently take the form of a feeling of dizziness, or of "something in the chest interfering with full inspiration." A deep inspiration is then taken and maintained for a period of ten, twenty or thirty seconds. At the same time choreo-athetotic movements of the limbs, bizarre attitudes or peculiar grimaces are common. Sometimes the patient stands up and throws back his head; others run their fingers through their hair. Roch [51] and Schmidt [56] quote a patient who would try to run away and conceal himself. Cyanosis is unusual, but may occur. In the severe cases, consciousness may be lost for a moment or two, as in our first and fifth cases. The inspiratory apnœa is terminated by a forced and often noisy expiration which is followed by a short period of compensating expiratory apnœa. Breathing is then resumed, each breath being of normal amplitude.

(3) *Respiratory Tics.*

(*a*) *Hiccough* is mentioned merely because discussion of its relationship with epidemic encephalitis would be beyond the scope of this paper.

(*b*) *Yawning.* Involuntary opening of the mouth is not an uncommon feature in the post-encephalitic Parkinsonian syndrome: during the last three months, three patients out of twenty-five observed by ourselves showed this symptom. Occasionally "mouth opening" occurs in paroxysms, is sustained for a few seconds and amounts in degree to a wide gape. Such a manifestation is tantamount to a yawn and may be included amongst the respiratory tics of post-encephalitic nature. An extreme instance is recorded in our third case and is illustrated by photograph (fig. 10). Other cases have been reported by Sicard and Paraf, Pardee, Hinds Howell, Abrahamson and Farquhar Buzzard.

(*c*) "*Soufflement.*" The French writers have used this word to denote tic-like expiration of air through the nose as though in order to dislodge a foreign body. (Babinski and Charpentier.)

(*d*) *Spasmodic cough.* One of the most distressing post-encephalitic "tics" consists in a constant, short, hacking, dry cough which persists during the daytime and often throughout the night. Pierre Marie gives the term "toux coqueluchoïde" to this cough. There are no pulmonary physical signs and examination of the larynx and pharynx is negative. This cough may be succeeded later by some other respiratory disorder as in Case 1 of our series.

These respiratory tics are particularly common in children after encephalitis. They tend to persist through the daytime, but show an increased frequency towards nightfall.

From the study of the recorded cases it is apparent that respiratory phenomena may arise at any stage of epidemic encephalitis. It does not seem possible to trace any association between the symptomatology of the original attack and the subsequent onset of respiratory disorders. Thus cases which were originally characterized by insomnia or delirium do not tend to develop subsequent respiratory disorders any more than cases showing lethargy. The myoclonic variety is known also to be followed occasionally by disorders of breathing.

Although respiratory disorders may occasionally constitute the sole late manifestations of encephalitis, it is more usual for other psychical and nervous after-effects to be present; association with inversion of the sleep rhythm is particularly common. The nature of the co-existing sequelæ does not appear to exercise any essential bearing on the nature or severity of the respiratory abnormality. It is difficult to gauge the

frequency of respiratory disorders during and after encephalitis. It is probable that the slighter dysrhythmias are not uncommon features, and it is only by careful observation of the respiration during sleep as well as in the waking state that many of them are discovered. Miss Anderson, in her study of forty children recovered from encephalitis, records "hyperpnœic" breathing in "many." Hinds Howell mentions three cases in his series of twenty-eight. Mlle. Lévy found ten instances of respiratory disorders out of 129 cases. On the other hand, out of 423 surviving cases of encephalitis recorded by Price [50], Bing and Staehelin [11], Palitzsch [46], Duncan [22], Shrubsall [57], Paterson and Spence [49], and Edgeworth [24], no mention whatever is made of respiratory upsets; we do not know, however, whether any such changes were looked for.

III.—The Pathogenesis of Respiratory Disorders.

It is not surprising that the earlier instances of respiratory disorders should have been regarded as "hysterical," but their close association with epidemic encephalitis, their persistence, and their uniform symptomatology render the diagnosis of hysteria untenable.

The influence upon respiration of changes in the acid-base equilibrium of the body and in the CO_2 tension of the blood is of course well known. It is difficult, however, to conceive of any such metabolic disturbances being the cause of so great a variety of respiratory disorders as we meet with after encephalitis. Any such alterations in the chemical composition of the blood must be regarded as the result rather than as the cause of derangements in the respiratory mechanism. It appears therefore that one must turn to the nervous control of respiration in investigating the morbid physiology of these phenomena.

When dealing with a disease characterized by scattered lesions throughout the central nervous system, the determination of the pathogenesis of a particular symptom is a matter of extreme difficulty—especially with the paucity of post-mortem evidence at our disposal. Consequently, discussion as to the causation of the respiratory disorders following encephalitis becomes, in our present state of knowledge, purely speculative.

Three main theories have been promulgated to explain these phenomena:

(1) The theory of peripheral origin. (Vincent, Bernard, Bériel.)
(2) The theory of thalamic origin. (Pardee.)
(3) The theory of medullary origin. (Roch and others.)

(1) *The Theory of Peripheral (Muscular) Origin.*

Bériel, 1921, suggested that tachypnœa after encephalitis is a compensatory mechanism which attempts to make up for the shallow breathing. This "micropnœa" he suggested was the result of rigidity of the intercostal musculature. This hypothesis is of course inapplicable to the great majority of cases—particularly those in which no trace whatsoever of Parkinsonian thoracic rigidity is observed.

Vincent and Bernard have drawn attention to the diminished expansion of the chest wall in many of these cases, their explanation being that the diaphragm was immobile. This suggestion is untenable in many cases, for normal diaphragmatic excursion can almost always be demonstrated upon the fluoroscopic screen.

Although it is highly improbable that disordered action of respiratory musculature plays any essential part in the pathogenesis of these disorders, it is possible that abnormal states in the thorax or abdomen may exercise a modifying influence. Thus abdominal myoclonus, or rhythmic movements in the diaphragm, are capable of superimposing a cogwheel or broken component to the respiration. Such is the probable cause of the *saccadé* nature of the breathing in our sixth case; the noisy and incomplete expiration in our seventh case is also the likely result of diaphragmatic spasm.

(2) *The Theory of Thalamic (Basal) Origin.*

Pardee states that the association of emotional instability, sleep disturbances and mask-like features are points in favour of a basal ganglionic lesion. Supporters of this view quote the researches of Lhermitte on pallidal lesions in which he found that the organic striped musculature subserving deglutition, respiration, and speech may be affected in addition to the skeletal muscles.

(3) *The Theory of Medullary (Bulbar) Origin.*

The majority of writers are inclined to regard the various respiratory disorders after encephalitis as manifestations of lesions of the respiratory centre situated in the medulla. The experiments of Hastings, Coombs and Pike [30] on cats have shown that by temporarily clamping the arteries to the medulla respiration becomes deeper and faster. It seems possible therefore that pathological changes in these blood-vessels may result in defective oxygenation of the bulb with consequent production of hyperpnœa. Reference has been made to the experiments of Rosenow who injected rabbits with streptococci obtained from the throats and

noses of patients showing dysrhythmias. A large proportion of the rabbits became affected with nervous symptoms, among which tachypnœa was prominent. Autopsy revealed changes most apparent on the ventral aspect of the medulla. The occasional influence of posture upon the appearance of tachypnœa recalls in many ways the behaviour of animals in which both vagi have been cut. Medullary changes, particularly in the pigmented cells of the dorsal nucleus of the vagus nerve, have been encountered in cases of post-encephalitis by Achard, Lévy, and by Foix [25] and Nicolesco. McAlpine [42], in an examination of the brains of two cases of post-encephalitis with tachypnœa, failed to discover changes in the medulla sufficient to account for the symptoms. Before discussing this theory, a short consideration of the anatomy and physiology of the respiratory centre is advisable.

The earlier writers placed this centre at various locations in the central nervous system. Thus, Christiani (1885) reported an inspiratory centre lying in the lateral wall of the third ventricle in the optic thalamus, just in front of the corpora quadrigemina and the commencement of the aqueduct. Vogt places the centre in the motor cortex; Lewandowsky in the posterior corpora quadrigemina, and Stern in the basal ganglion. The work of Legallois and Flourens, however, has established that part at least of the central respiratory mechanism lies in the medulla in close association with the nucleus of the vagus. The more recent work of Lumsden [35] has shown that the respiratory centre is a complex structure made up of at least four component parts:—

(*a*) A primitive "gasping" centre situated in the region of the calamus scriptorius, the nature of which is probably vestigial.

(*b*) An area in the region of the striæ acousticæ, the function of which is inspiratory. This may be called the "apneusic centre."

(*c*) An area in the upper part of the pons which inhibits (*b*). This is the "pneumotaxic centre."

(*d*) An expiratory centre located just below the level of the striæ acousticæ.

These centres, he showed [36], depend for their functional activity upon the CO_2 tension of the blood.

Rosenthal has proved experimentally that the central respiratory mechanism is capable of independent existence even when cut off from outside neuronic influences. Under normal conditions, however, many extraneous factors continually exercise control over the respiratory centre. Thus afferent impulses from the vagal distribution and from

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all visceral and cutaneous areas, and particularly the fifth nerve, are capable of altering the rate and rhythm of respiration. The higher cortical control of respiration is shown by the power of deliberately inhibiting or altering normal breathing up to a point. Spencer [59] has demonstrated that there are at least four cortical paths along which these psychomotor impulses may proceed :—

(1) A path leading from the motor cortex through the genu of the internal capsule probably conveys the voluntary impulses controlling respiration. Stimulation produces breath-holding. (2) A tract arising from the under surface of the frontal lobe and proceeding along the olfactory limb, past the infundibulum to the mesial aspect of the lower part of the optic thalamus near the third ventricle and so to the medulla. This is the "arresting path." Camus [18] noted that operations in the hypophyseal region frequently cause a cessation of breathing, due probably to interference with this path. (3) An "accelerating tract" leaves the sensory cortex, and passes through the lenticular nucleus to the tegmentum pontis and medulla. (4) A pathway, entering from the junction of the olfactory bulb and tract, into the uncus, passing behind the optic tract to the crus cerebri, and then mesially towards the upper border of the pons ; stimulation of this tract produces "over-inspiratory clonus."

There is an obvious difficulty in determining on theoretical grounds alone the site of the causal lesions in these respiratory disorders. Moreover, there appear to be but few records of post-mortem examination of the brain in such conditions. Defect in the automatic or involuntary mechanism of breathing is the most obvious common factor ; in almost every case the ability of the subject to control voluntarily the respiratory dysrhythmia persists though only to a limited extent. Apparently there is an integrity of the voluntary mechanism of breathing which we believe runs in the descending motor tract (1) above. It seems probable, therefore, that either the pneumotaxic centre is the site of disease or one or other of the psychomotor supranuclear mechanisms. A lesion of the pneumotaxic centre would be unlikely to spare the other important structures which are in such close proximity, and yet one knows that clinically pontine symptoms rarely co-exist with post-encephalitic respiratory upsets. Again, after experimental ablation of the pneumotaxic centre in animals, the breathing takes on a well-defined gasping character which is spoken of as "apneusic." This type of respiration we do not meet with after encephalitis.

Most writers have laid stress upon the influence of emotional

fluctuations over the respiratory disorder. Thus fear, excitement, or embarrassment augment the symptoms, whilst isolation, sedative drugs and indifference diminish them. The influence of sleep is another point of importance; in almost every case sleep has a marked effect upon the dysrhythmias, either by intensifying them, or, much more commonly, stopping them. Two other striking features must be emphasized: on the one hand, the frequency of psychical changes in connection with respiratory upsets, and on the other the rarity of pontine or bulbar symptoms. The relative frequency of breathing disturbances amongst children and young adults tends to implicate the later-developed and less stable psychomotor paths. These points all favour strongly the hypothesis that the paths conveying the higher involuntary cortical influences are at fault rather than the actual medullary nuclei.

The widespread extent of these psychomotor tracts accounts for the varied features of the respiratory disorders, and also for the diversity of accompanying symptoms. Thus proximally the sensorimotor cortex, the olfactory bulb and the ventral aspect of the frontal lobes form the starting point of these pathways, and lesions in these localities may account for the additional features of mental disorders and abnormal nasal sensations. When traced downwards these tracts tend to converge mesially towards the third ventricle, in the region of which lesions responsible for the adiposity-polyuria syndrome may be found. The tracts pass through the corpus striatum where are found the lesions of Parkinsonism. In this way one may reconcile the co-existence of disorders of respiration with every variety of the known sequelæ of encephalitis.

In one type of case only is a bulbar lesion the probable cause of respiratory embarrassment. We refer to the rare cases showing during the acute stage all the manifestations of a progressive bulbar lesion (dysarthria, dysphagia, hypoglossal palsy and dyspnœa). Such cases are usually fatal and bear little or no resemblance to the other forms of respiratory upset.

The occurrence of tetany, as we have mentioned, is to be expected whenever tachypnœa is accompanied by respirations of increased amplitude. Tetany in these cases is identical with the experimental tetany following deep breathing. The over-oxygenation of the lungs in such cases tends to wash away CO_2 from the circulation, and an increased blood alkalinity results with a reduction of the alkali reserve. This finds expression clinically in increased nervous irritability passing into actual tetany.

Consciousness may be lost during the respiratory disorders of encephalitis under two circumstances: (*a*) whenever inspiratory apnœa is maintained up to the point of mental confusion (as in our first case); and (*b*) whenever the hyperpnœa which is productive of tetany is maintained for an unusually long period (as in our fifth case).

IV.—Prognosis and Treatment.

Two main questions naturally arise in dealing with the prognosis of the respiratory phenomena. First, is the appearance of respiratory symptoms of itself a feature of serious import? and secondly, how long do the respiratory disorders persist? The former question is particularly difficult to answer owing to the paucity of statistical information on this point, but there is a certain amount of evidence to suggest that the appearance of tachypnœa as a sequel to encephalitis is of grave outlook in the older patients, particularly when associated with pyrexia. McAlpine has recorded two cases in which this phenomenon was rapidly followed by death, and Mlle. Lévy has described in her book four cases in which this mode of death occurred. The duration of these symptoms seems in the majority of cases to be indefinite, although now and again a case will improve spontaneously. Thus Hinds Howell's patient with tachypnœa arising during convalescence got completely well after some months and returned to work. One case of Parker's and one of Mlle. Lévy's improved spontaneously after leaving hospital. The majority of cases, however, tend to persist with unabated violence for an indefinite length of time. They show no tendency to progress, however. This prognosis apparently holds good for all the varieties of respiratory disorders.

No treatment is known which will definitely improve these disorders. A. J. Hall [28] recommends the inhalation of pure oxygen; sedative drugs are mildly palliative when given in full doses; of these, injections of hyoscine and luminal by the mouth are the most efficacious. Bromides, conium, paraldehyde, chloral, chloretone and other such drugs are of lesser value. On theoretical grounds it seems possible that the intravenous administration of acid solutions may be capable of reducing hyperpnœa.

Treatment by suggestion is by no means curative, but at times will improve the patient by re-establishing some degree of moral control. The alarming nature of some of these phenomena—particularly the breath-holding types—often terrify the patient and this tends to increase the violence and frequency of the attacks. A certain amount of helpful

suggestion will do much in these cases to reassure the patient and bring back his self-confidence. The clumsier forms of psychotherapy—such as suggestion by hypnosis, anæsthesia, or faradism are of little or no avail.

V.—Clinical Cases.

Case I.—*Attacks of breath holding: inversion of sleep rhythm: psychical disturbances, following encephalitis.*

H. B., male, pupil teacher, aged 16, was admitted to the National Hospital, Queen Square, under Dr. Aldren Turner, on September 28, 1924, for "fits" of one week's duration.

Previous health.—Patient was a healthy and intelligent boy until the age of 14. Measles at 6 and influenza at 10 were the only illnesses of his childhood. At the age of 14 he underwent an operation for chronic appendicitis. The boy's mother said that he was "never the same afterwards." He became nervous and apprehensive; headaches became frequent, and he often complained of dizziness. He was working hard at the time as a pupil teacher, and his parents, thinking that study was upsetting him, got him an appointment as a clerk to a firm of nursery gardeners.

Two weeks before Easter, 1924, patient was noticed to be drowsy; on several occasions he dropped off to sleep over his meals and while at work. No other symptoms were complained of until two weeks later when he began to be restless. He "was unable to settle anywhere: always had to be up and doing." At the same time he complained of headache, and his temperature was found to be raised. He was sent to bed and delirium followed for four days and nights. In his delirium he rambled incessantly about his work; he would try to get out of bed and go through the pantomime of planting shrubs and tying on labels. His illness, which confined him to bed for three weeks, was diagnosed as "meningitis." There was at no time any diplopia or squint.

Convalescence was slow; patient frequently complained of headache and his dizziness became worse. Later, he became sleepless at nights, and was unable to fall asleep until dawn: he slept deeply however throughout the mornings, not waking up until lunch time.

A month before admission to hospital he began to have a persistent short hacking cough, which lasted almost throughout the twenty-four hours. No abnormality was found in the lungs, and the cough was regarded as "nervous" in origin. It lasted about three weeks.

One night, a week before admission, patient found himself "sitting up in bed, with a start every five or ten minutes." This continued all night until 7.30 in the morning, when he fell asleep. He then got up, and when going out into the coal-shed suddenly collapsed in what was thought to be a "faint." The duration of the attack was apparently only momentary. Two days later patient went up to relatives in London. The next day the boy had

three similar "turns" and six the following day. Then the "turns" commenced in rapid succession and he was admitted into hospital three days later.

The maternal grandfather has been an inmate of an asylum for ten years with dementia, secondary to melancholia. Otherwise *nil ad rem* in the family history.

Condition on admission.—The patient is a healthy-looking young man of fair complexion and good colour. Whilst lying in bed there is observed a series of abnormal respiratory movements, accompanied by involuntary purposeless gestures of the body and limbs. These attacks recur about every thirty seconds.

Each attack begins with a number of deep and laboured respirations, which increase in depth and intensity, and are sometimes accompanied by a short, hacking cough. These are rapidly succeeded by a period of apnœa, in which the chest is held, as if by a voluntary effort, in a state of full inspiratory distension. During the apnœic phase, which lasts for several seconds, the face rapidly becomes cyanosed and the musculature of the chest is in a state of tonic spasm and fixation. Shortly after the onset of the apnœic phase the forearms are flexed and pronated, the fists tightly clenched, the neck and back arched into an attitude of partial opisthotonos and the lower limbs extended, more especially that on the right side.

There now follows one of the most remarkable features of the attack, viz., involuntary, extravagant and purposeless gestures, such as rubbing the hands upon the chest, clawing the air, or unclenching and clenching the fists. The cyanosis increases, so that the veins stand out prominently on the forehead and the eyes bulge. The tongue is protruded between the teeth, but is never bitten, being protected by an inversion of the upper lip.

The paroxysm seems now to have attained its maximum, for the apnœic phase is terminated by a long expiration, which is accompanied by facial distortion of a remarkable kind, the mouth being opened widely, the eyes deviated to the right and the head retracted. Sometimes the left orbicularis palpebrarum is closed during the grimace. At the same time the congestion of the face becomes replaced by intense pallor. After a few seconds of expiratory apnœa breathing returns in gasps. The whole cycle occupies twenty to thirty seconds in time (see figs. 2, 3 and 4).

These attacks succeed each other very rapidly, as many as thirteen being counted in a space of five minutes. Consciousness has been lost on only a few occasions, and then was momentary. The violence of the tonic spasm is sometimes sufficient to cause him to fall unless supported. When in the stage of inspiratory apnœa conversation is inhibited, but the boy sees and hears perfectly well, and can resume the thread of the conversation which has been thus interrupted.

When questioned why he holds his breath he replies, "I can't help it." The attacks follow each other in such rapid succession that at no period was the respiration ever normal. During sleep, however, respiration becomes

FIG. 2.—Photograph of Case I taken during the phase of inspiratory apnœa. The tongue is seen protuded between the inverted lips; the face is rapidly becoming congested.

FIG. 3.—Same patient as in fig. 2 taken at the moment of the forced expiratory effort. The face is seen to be distorted into an extraordinary grimace, the mouth opened widely, the eyes deviated upwards and the head thrown back. The facial congestion has given place to extreme pallor. Note the clenching of the fists.

quiet, regular and normal in rate (20), but the amplitude of each breath is shallow, thoracic expansion being minimal.

Physical examination: circulatory system.—In the interparoxysmal periods the pulse is of moderate rate and tension and is regular in force and frequency. The vessel wall feels normal. Blood pressure measures 120. During the height of the apnœic period the radial pulse is imperceptible.

FIG. 4.—Same patient taken during the third and final stage of the respiratory cycle, viz., during the period of expiratory apnœa. The head is slightly turned to the left; the left side of the face is in a state of spasm. Both fists are clenched and the left arm is in the process of being flexed and externally rotated.

The area of cardiac dulness is normal. On auscultation the heart sounds are pure and regular. No murmurs can be detected. During the height of the apnœic period, the heart beat becomes inaudible and the apex beat impalpable.

Electro-cardiography reveals a normal heart beat. During the paroxysms the curve is obscured somewhat by somatic movements, but the regular occurrence of S waves reveals that the heart continues without alteration in rate and regularity (see fig. 5).

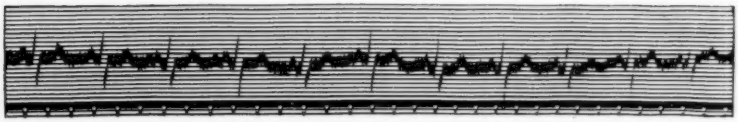
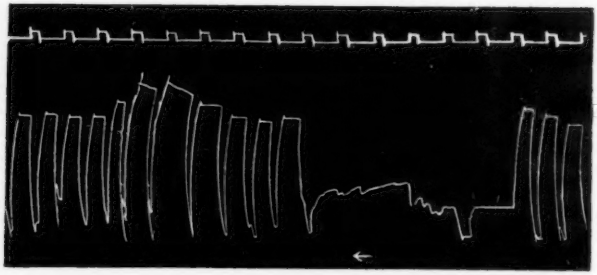


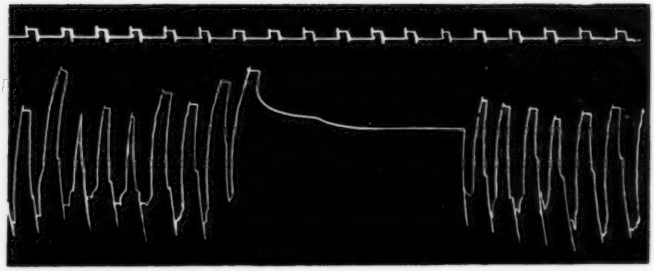
FIG. 5.—Electrocardiagram of Case 1 showing ventricular contractions, which are normal in rate and rhythm. A record taken during one of the breath-holding spells is somewhat marred by somatic deflections, but it is quite clear that the 's' waves are normal in appearance.

x *y* *z*



x *y* *z*

x *y*



FIGS. 6, 7 and 8.—Pneumograms of Case I showing respirations irregular in time and spacing, interposed with periods of apnœa. (*x*) apnœa in almost full inspiration, (*y*) forceful expiratory effort, (*z*) short spell of acapnia.

Alimentary system.—Tonsils, teeth and gums are healthy. The tongue is moist and clean. No difficulty in swallowing. The abdomen moves well on respiration and no peristalsis, distension or tumour can be seen; there is no tenderness, tumour or mass on palpation.

The bowels act regularly every day. During the stage of apnœa the abdominal musculature takes part in the general tonic spasm.

Respiration.—Laryngoscopic examination (Mr. Theodore Just). "Cords normal. Glottis adequate. On phonation there is some loss of adduction of the posterior ends of the cords, immediately after the sound has been made. Both cords move freely on respiration. The aspect of the larynx suggests a functional loss of tone posteriorly."

The respiratory cycle is graphically represented in the following charts (figs. 6, 7 and 8). The respiration rate (taken during quiescent periods) is 20.

Examination of the chest reveals no abnormality on percussion or auscultation. The breath sounds are pure, vocal resonance and fremitus are normal, and there are no added sounds. Skiagraphy of the chest shows no abnormality; the two halves of the diaphragm move synchronously.

Endocrine system.—There is no abnormality of growth or stature. Hands and feet are normal in size and shape. There is no thyroidal swelling; no abnormal pigmentation; has had no beard; pubic hair is very scanty for his years. There is no hair on the legs, arms or trunk, but axillary hair is normal.

Genito-urinary system.—There is no polyuria. Urine is acid, sp. gr. 1020: albumen, sugar, pus and blood are absent. Total acidity = 300 (expressed in terms of $\frac{N}{10}$ alkali).

Testes and epididymis normal. Sphincter control was normal on admission, but after about a month in hospital patient became a little careless in his habits which later amounted to actual incontinence of fæces.

Central nervous system.—Memory, intelligence and cerebration appear very good. Orientation is correct for all spheres. Is nervous in disposition and seems to be unduly euphoric, i.e., making light of his condition and insisting that it is becoming much better when it is obviously not changing. He is not unduly introverted; co-operates well, is a good witness and gives a good account of his symptoms.

He has had no fits, delusions or hallucinations.

Sleep: Patient is troubled with severe insomnia, rarely falling asleep before the small hours of the morning. On the other hand, he remains asleep throughout the morning until noon. During sleep the paroxysms cease, and the respiration becomes quiet and regular.

Speech is normal, though the voice is husky and broken in the characteristic manner of late puberty.

No abnormality was detected in the domain of the cranial nerves other than that convergence is not well sustained in the left eye when the fixation point is nearer than 4 in. to the nose, and occasionally on lateral ocular deviation there is a rapid horizontal rhythmic nystagmus which is well sustained. Arms and legs are normal in attitude and appearance. The outstretched hands show no

tremor. There is no abnormality in muscle tone, but during the attacks the voluntary musculature goes into a state of tonic spasm, the attitude being that of flexion in the upper and extension in the lower extremities.

Reflexes.—All the tendon-jerks are normal. Plantar stimulation gives a flexor response throughout the periods of apnœa. There is no clonus and no

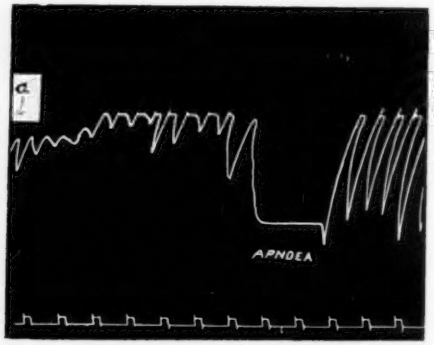


FIG. 9 (*a*).

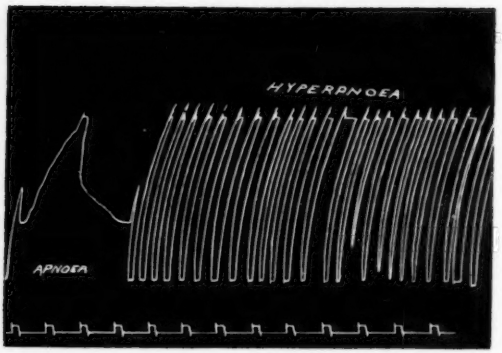


FIG. 9 (*b*).

FIGS. 9 (*a*) and 9 (*b*).—Showing the effect of continuous inhalation of oxygen in Case I. The oxygen was turned on at the point 'a.' The respirations at once become shallow and rapid. After the first period of apnœa, the respirations increase in both amplitude and rate (*b*). There is no marked effect on the apnœic pauses.

loss of sphincter control. The oculo-cardial reflex was absent, i.e., pressure on the eyeballs had no retarding effect on the heart beat.

Gait.—During the inter-paroxysmal periods the gait is normal, but the patient may stagger and sometimes fall unless supported during the stage of apnœa.

The cerebrospinal fluid revealed no abnormality with regard to cytology, protein content and the Lange or Wassermann tests. Blood Wassermann reaction was negative. Serum Ca content = 11 mg. per cent.

Progress whilst in hospital.—The breath-holding spells persisted throughout his stay in hospital. The patient was able voluntarily to inhibit the paroxysms for a few minutes only. They ceased during sleep and became less during meals, under the influence of hyoscine or whenever the attention was distracted. Chloroform anæsthesia failed to bring about a permanent cessation of attacks.

After some weeks in hospital it was noticed that the patient was becoming a little careless in his personal habits, and sphincter control was at times defective.

Three months after admission patient gradually began to give evidence of hallucinatory and religious delusions: on one or two occasions he declared that "God had come and spoken to him." He was also in the habit of writing out long and rambling prayers offered up on behalf of the hospital staff and his fellow-patients. The carelessness of his habits at the same time increased so as to amount to actual incontinence.

The patient gave evidence of showing some exhaustion as a result of so many continued attacks, but the degree of debilitation was unexpectedly slight.

Influence of therapy.—There was no definite improvement in the patient's condition in spite of vigorous treatment with sedatives, as bromides, hyoscine, luminal, &c. Treatment by suggestion completely failed to relieve the patient. His paroxysms were unaffected by making him inhale amyl nitrite, CO_2 or nitrous oxide—anæsthesia being obtained by the last measure only after a prolonged inhalation. Inhalation of O_2 had no effect upon the apnœa, but the respirations became markedly shallower and more rapid (see fig. 9 (*a*) and (*b*)).

CASE II.—*Parkinsonian syndrome: wide involuntary opening of mouth coming on in paroxysms three-and-a-half years after the acute attack of encephalitis.*

H. W., male, aged 26, was admitted to the National Hospital, Queen Square, on December 6, 1924, under the care of Dr. Kinnier Wilson.

In January, 1920, the patient had an attack of acute epidemic encephalitis (ocular symptoms, lethargy). The acute phase lasted four to five weeks. Six months later tremor appeared in the left arm and a definite Parkinsonian syndrome gradually developed.

In September, 1923, he began to show involuntary movements of the lower jaw, which would open widely as though yawning. There was no accompanying pain, but occasionally the patient found difficulty in closing it. Dysphagia is also present to a slight degree.

Physical examination.—Patient is very emaciated. The appearance and attitude are typical of Parkinsonism; the forearms are held pronated-flexed across the chest in the characteristic manner, but no tremor is visible.

Every minute or so the patient's mouth will open involuntarily to an extraordinary extent—"like the mouth of a hippopotamus." Each condyle of the jaw rides forward on to the eminentia articularis, and one can see well down the pharynx as far as the epiglottis (see fig. 10). These involuntary movements are irregular both in frequency and extent, varying from a minor degree to the maximal possible. The mouth is kept open for periods varying from a few seconds to almost a minute. Frequently the patient was compelled to put up his hand to close his mouth. The movement is quite involuntary and painless, but interferes with eating. During sleep no movements occur.

FIG. 10.—Photograph of Case 2 illustrating the wide involuntary opening of the mouth.

The pupils are equal, reacting briskly to light, but sluggishly, on accommodation. Ocular movements are jerky in character and convergence is absent. There is marked lid retraction. The face is wooden during repose. No tremor of tongue or face.

Muscular tone is definitely increased in his arms and legs—the rigidity being of the cogwheel variety. All movements are possible, but are very slow in execution. There is but very slight tremor in the forearms.

Sensation is normal. Reflexes are normal. There is a loss of associated movements at the shoulders; the steps are small and the gait is stiff and festinant.

Speech.—Monotonous: patient tends to delay over some syllables, and there is hurrying over others.

CASE III.—*Parkinsonism; inverted sleep rhythm; nocturnal dyspnœa and breath-holding spells.*

V. W., female, aged 15, was admitted to the National Hospital, Queen

Square, under the care of Dr. Birley. Seven months previously she had an attack of acute encephalitis (lethargy, diplopia, headache, twitching right side of mouth).

Whilst in hospital she exhibited diurnal lethargy with nocturnal restlessness and a slight twitching of the corner of the mouth with involuntary protrusion of the tongue. Speech was stammering in type. Some degree of spasmodic torticollis was present.

Pupils were unequal with normal reactions; convergence was good. There was slight ptosis of the left eyelid and slight facial asymmetry. There was some increase of tone, with weakness and clumsiness in the left arm, hand, and leg.

Babinski's sign was positive in the left foot. The oculo-cardiac reflex was absent, but the cilio-spinal reflex brisk.

Gait was shuffling in character; there was a loss of associated movements at the shoulders. The cerebrospinal fluid was normal in all respects.

During the day patient's respiration was normal in character. At nighttime, whilst in bed she complained of difficulty in getting her breath, and she moved restlessly about in bed. When actually asleep, her respiration was interrupted by irregular apnœic pauses and sighs, accompanied by irregular torsion movements of the limbs.

CASE IV.—*Tachypnœa; myoclonus; mild Parkinsonism.*

E. S., a butcher, aged 19, attended the Out-Patient Department of the National Hospital, Queen Square, under the care of Dr. Gordon Holmes, on January 16, 1925, and was admitted under Dr. Collier on February 9, 1925.

In March, 1924, he had an attack of encephalitis lethargica with myoclonus, delirium and insomnia. His recovery was never complete, and the myoclonic movements of the limbs persisted. The insomnia, however, gave place to lethargy. He became dull in mentality.

Physical state.—Patient stands in a bowed attitude and some jerky movements are apparent in both arms, especially the left. His face is expressionless during repose. Respiration is rapid (40), irregular and rather noisy. Patient is aware that his breathing is hurried, but it causes him no distress.

Cranial nerves.—Face rather wooden. Pupils: the right is larger than the left, they react sluggishly on accommodation. Eye movements and other cranial nerves unaffected.

Motor system.—Tone normal, and no loss of power; myoclonic movements are visible in both trapezii, both pectorals and in the left deltoid. Co-ordination is accompanied by a slight intention tremor.

Gait.—There is a loss of automatic movement at the shoulder-joints, but it is otherwise normal.

Reflexes normal.

Respiration.—Breathing is rapid (40) and rather noisy. The respirations are irregular, both in amplitude and time. Inspiration is short and abrupt; and is followed by a short inspiratory pause; expiration is slow and is pulled up

quickly by the onset of the succeeding abrupt inspiration (see fig. 11 (*a*) and (*b*)). Myoclonic movements of the upper recti abdominis and of the shoulder muscles accompany respiration and synchronize with the onset of each inspiration. These movements continue when the patient voluntarily holds his breath. Chest expansion is fair. There is no rigidity of the thoracico-abdominal musculature. The accessory muscles of respiration are not acting.

During sleep the breathing is even faster (60 per minute) and noisy in character. Inspiration is nasal and strident, and is longer than expiration. There is no pause between the inspiratory and expiratory components, but after each exhalation there is a momentary period of apnœa. The myoclonic movements are not apparent during sleep.

Radioscopic examination of the thorax shows full excursion of the diaphragm with no asynchrony between the two halves. At the end of expiration, however, diaphragmatic elevation tends to become a little broken in character.

CASE V.—*Paroxysmal tachypnœa with deep breathing, tetany and attacks of unconsciousness.*

D. I. E. B., female, machinist, aged 22, was admitted to the Hospital for Epilepsy and Paralysis, Maida Vale, under the care of Dr. Campbell Thomson (later Dr. McAlpine), in May, 1924.

In July, 1923, she had acute encephalitis whilst in Australia, with insomnia, restlessness, choreiform movements, diplopia and delirium. Her convalescence was protracted and marked by obstinate insomnia.

In February, 1924, attacks of deep, rapid breathing came on, often lasting all day; there was no accompanying distress. Later, the patient noticed tingling and cramps in her hands and feet and in the left side of the face; she had to rub them "in order to get the circulation back." In March, 1924, paroxysms of polypnœa were now frequently followed by "fits," in which she became very rigid and cyanosed and lost consciousness for a few seconds. These attacks were nearly always nocturnal; there was no accompanying tongue biting or involuntary micturition.

Present condition.—Nervous temperament. Breathing at one time normal, at other times deep and rapid [28] but without any discomfort.

During the tachypnœic periods, the thoracic expansion is increased and the alæ nasi and sterno-cleido mastoids participate in the act of respiration. When observed during sleep, breathing is normal in rate (18) and regular but unduly shallow. Moderate cyanosis is present, but when awakened hyperpnœa rapidly ensues and the colour becomes normal.

When the panting is severe patient is observed to get cramps of the extremities and the hands take up the typical accoucheur's position.

Cranial nerves.—Pupils equal, sluggish reaction to light, none on accommodation. Convergence is poor. Nystagmus on upward and lateral ocular deviation.

Chvostek's sign is readily elicited, particularly on the left side of the face.

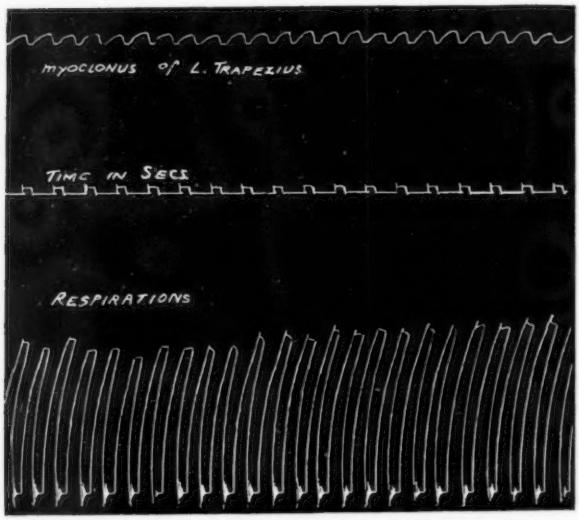


FIG. 11 (*a*).

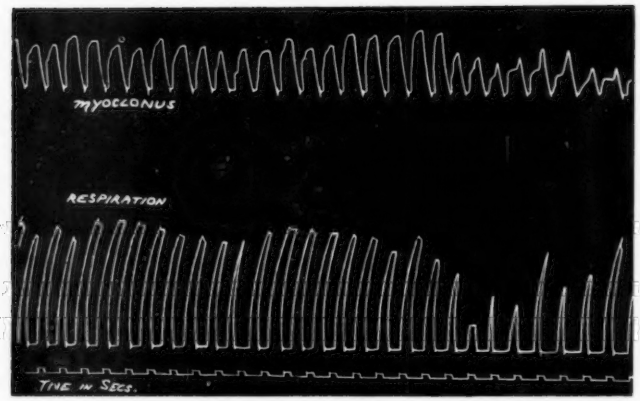


FIG. 11 (*b*).

FIGS. 11 (*a*) and 11 (*b*).—Tracing taken from Case IV recording simultaneously myoclonic movements of the left trapezius and respiration. Note the rapid rate of breathing, and also the synchrony between the myoclonus and the respiration.

The left side of the face is weaker than right and there is slight tremor of the tongue.

Motor system.—No abnormality in power or tone, no wasting, no involuntary movements. Trousseau's sign is positive and some myotatic irritability is present.

Reflexes.—All normal except the the left plantar response, which is equivocal.

Heart and lungs normal.

Laboratory findings.[1] Urine 1020, acid, no albumen, sugar, pus or blood.

	June 4	July 3	Nov. 11
	(During a quiescent period)	(Taken during a spell of hyperpnœa)	
Plasma pH	7·25 ..	7·57 ..	7·49
Plasma bicarbonate ..	45·00 ..	35·64 ..	49·00

CASE VI.—*Inverted sleep rhythm; Parkinsonism; paroxysmal tachypnœa with shallow, cogwheel respirations.*

A. G., male, aged 25, was admitted to the Hospital for Epilepsy and Paralysis, Maida Vale, under Dr. Anthony Feiling.

The family history and previous health contain nothing relevant.

In March, 1924, he had an acute attack of epidemic encephalitis with lethargy, delirium, vomiting and diplopia, followed almost immediately by generalized tremor and stiffness. In June, 1924, there was slight relapse with return of delirium, followed by inversion of the sleep rhythm, pains in the eyes, pins and needles in arms and chest and pressure pain on the top of his head.

At the same time difficulty in breathing developed; the patient says that he cannot breathe deeply without considerable effort and that he is compelled to breathe rapidly in order to get enough air into his lungs. He also complains of "pulsation of the nerves" which causes his respiration to be jerky; this pulsation is "like a slight headache beginning in the head and passing down over the face and upper part of the chest, and down the arms as far as the wrists, where it ends in a sensation like a nettle sting."

Physical state.—His face is mask-like with double pseudoptosis. When lying in bed asleep there are constant twitching and semi-purposive movements of the hands, which are not present during the waking state.

His pupils are equal but react very sluggishly to light and accommodation. Convergence of his right eye is poor, and upward and downward ocular deviation are limited.

Speech is slightly dysarthric with a distinct nasal quality. There is slight weakness of his right lower face and paresis of the right side of the tongue and palate.

Motor system.—Both hands are tremulous, muscle tone is somewhat increased but motor power and co-ordination are unaffected. The patient's gait

[1] Carried out at the London Hospital, and reproduced through the courtesy of Dr. George Riddoch.

and attitude are characteristic of Parkinsonism. Reflexes are normal and there is no impairment of sensation.

Examination of the cerebrospinal fluid shows 1 to 2 cells per c.mm.; total protein equals 0·045 per cent., and the Wassermann and Nonne-Apelt tests are negative. Lange's colloidal gold reaction gives 1133321000.

Respiration is shallow, rapid (24 to 70), irregular in time and amplitude, and rather noisy. Inspiration is normal, but expiration is cogwheel or broken in character. Inspection of the chest shows that the upper thorax is immobile, becoming fixed in a position midway between inspiration and expiration. Breathing is almost entirely diaphragmatic, and the lower intercostal spaces are indrawn to an unusual degree. The epigastrium bulges during inspiration, and during the expiratory phase the jerky character of the breathing can be readily seen and felt (see fig. 12). No accessory muscles of respiration are active except the alæ nasi. The tachypnœa is paroxysmal in appearance, but the cogwheel nature of the expiration is constant. The respiratory disorder tends to become worse towards nightfall.

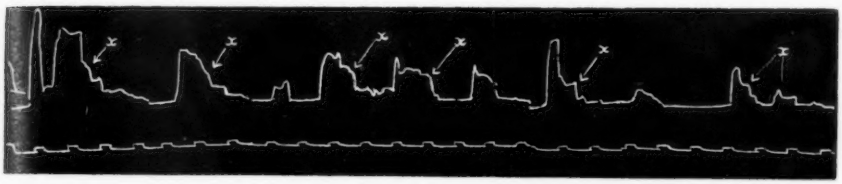


FIG. 12.—Tracing taken from the lower costal cartilages of Case VI showing shallow respirations, which are irregular in time and amplitude. Note the peculiar broken or "*saccadé*" character of the expiratory component as shown by the down-stroke of the respiratory curve *x*.

Fluoroscopic examination of the chest reveals that the diaphragm is freely mobile on both sides and synchronous in action. The diaphragm, however, is seen to rise during expiration in a series of rapid jerky movements.

CASE VII.—*Irregular tachypnœa occurring during the acute phase of myoclonic encephalitis and persisting as a residual symptom.*

W. E., aged 55, stoker at a gas works, was admitted to Southmead Hospital, Bristol.

Patient was attacked six weeks previously with pains in the head, delirium, lethargy and diplopia. His gait was staggering in character. He was treated for acute epidemic encephalitis by Professor Nixon at the Bristol Royal Infirmary.

On admission to Southmead Hospital he showed a definite immobility of expression. Muscular power in his arms and legs was diminished with a slight increase in tone in the muscles. The pupils and cranial nerves were normal.

There was a constant slight to-and-fro nodding movement of his head, and rhythmic myoclonic twitching of his left shoulder.

Reflexes and sensation were normal.

Sleep.—Marked insomnia but no diurnal lethargy.

Respiration.—Irregular tachypnœa (26 to 64 per minute) with noisy *saccadé* and shallow respirations "as though the diaphragm were in a state of tremor." Breathing was at no time normal but tended to become worse in paroxysms. The tachypnœa persisted during sleep.

He left hospital six months later, somewhat improved, but the respiratory upset was still present.

We beg to thank the Medical Superintendent of Southmead Hospital for permission to reproduce this case.

VI.—Summary.

An outline is given of the literature dealing with respiratory disturbances associated with epidemic encephalitis, and seven illustrative cases are described in detail. It is clear that these manifestations cannot be regarded as accidental or "hysterical" phenomena, but that they constitute a very definite clinical entity playing an important rôle in the symptomatology of the disease.

The various disorders of respiration are of the most diverse nature, ranging from simple alterations in time to the most bizarre distortions of the normal mechanism. It is proposed to adopt the following classification which comprehends all the types that are on record :—

(1) Disorders of the respiratory rate.

(2) Dysrhythmias, or disorders of the respiratory rhythm.

(3) Respiratory "tics."

Any combination of these groups may co-exist.

Respiratory phenomena may appear as symptoms of the acute attack, as residua or as remote sequelæ. They may constitute the sole after-effect, but more commonly they are associated with other well-recognized physical or psychical sequelæ. Children and young adults are particularly prone to show abnormal breathing, and inversion of the sleep rhythm and disorders of conduct very commonly co-exist.

The theories of bulbar, thalamic and peripheral origins are discussed; these hypotheses, however, fail to explain all the known facts and are obviously inadequate. Emphasis has been placed upon the frequent association of respiratory derangements with disorders of sleep and of conduct. The influence of sleep and of the emotions upon the breathing is very marked, and in the majority of cases a temporary inhibition of the disorder can be produced by voluntary

effort. *It is probable, therefore, that the pathogenesis of these phenomena lies in a derangement of the involuntary psychomotor control of respiration, which is maintained by various cortico-pontine pathways, capable of anatomical demonstration. The lesion, therefore, is placed at a level higher than the so-called respiratory "centres."*

Prognosis is serious when respiratory abnormalities appear during the acute phase, a large proportion of such cases proving fatal. When appearing as sequelæ, however, the exact outlook is unknown; the majority of such cases seem to persist unchanged for an indefinite period. No treatment is known which is of any avail.

It is probable that the minor forms of respiratory disorder are more common features of post-encephalitis than is generally realized.

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A CLINICAL STUDY OF INCREASED INTRACRANIAL PRESSURE IN SIXTY CASES OF CEREBRAL TUMOUR.

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THIS paper[1] represents an attempt to analyse the signs and symptoms of increased intracranial pressure manifested by a series of sixty cases of cerebral tumour. The term "cerebral tumour" is used to include, besides neoplasms, certain localized infective conditions which give rise to increased intracranial pressure. In twenty-four cases the precise situation and extent of the tumour was ascertained at autopsy, in fourteen other cases the site of the tumour was verified during operation, but in the absence of autopsy its extent could not be accurately estimated. In the remaining twenty-two cases there was no autopsy, and operation, if performed, gave no reliable information as to the site of the tumour. The first two groups are described as "verified" cases, the last group as "unverified." Wherever the situation of the tumour has had to be taken into consideration conclusions have been drawn from verified cases only; and the investigation of the symptomatology and ætiology of the hydrocephalus has been based on those cases only which came to autopsy.

The nature of the tumour was ascertained in thirty-four cases as follows:—

Glioma	21
Glio-epithelial papillary carcinoma	1
Endothelioma	1
Multiple neuro-fibromata	1
Angeioma	1
Multiple mixed-cell sarcomata	1
Secondary to intrathoracic neoplasm	3
Aneurysm	1
Tuberculoma	2
Hydatid cyst	1
Cystic tumour of infundibulum	1

[1] Part of a thesis accepted for the degree of D.M.Oxon.

The Intracranial Pressure and the Blood-pressure.

It is necessary at the outset to give a brief summary of the present state of our knowledge of the complex conditions of the intracranial pressure. It was established by Munro and Kellie that the cranial cavity in the adult is relatively fixed in volume and is completely filled by brain, cerebrospinal fluid and blood. The brain itself is incompressible, but variation in the amount of either of the fluid elements is compensated for by alteration in the volume of the other. The intracranial pressure, i.e., the pressure exerted by the brain on the interior of the skull, is a product of the blood-pressure and undergoes fluctuations, being increased by the rise of blood-pressure in cardiac systole and by expiration which diminishes the venous outflow from the intracranial sinuses. Since the cerebrospinal fluid normally circulates freely over the surface of the brain the pressure of the cerebrospinal fluid and the intracranial pressure must be the same; and this has been found by different observers to be about 120 mm. of Ringer's solution.

The work of Leonard Hill [5] on the cerebral circulation, published in 1896, remains of fundamental importance, and has formed the basis for all subsequent investigation of this subject. Hill concluded from his observations that the pressure of the cerebrospinal fluid could never be higher than the blood-pressure in the intracranial sinuses, but Weed [11] has compared the pressure of the cerebrospinal fluid in the cisterna magna with the venous pressure in the sagittal sinus at its entrance to the torcular, and concludes that "while dependent upon both intracranial arterial and venous pressure, and while influenced passively and in the same direction by both, the pressure of the cerebrospinal fluid may be considered to be relatively independent of both in that normally it maintains an individual fairly constant level far below that of the intracranial arteries and somewhat above that of the intracranial veins."

This suggests an inquiry as to why the intracranial veins do not collapse, if they are subjected to a pressure of cerebrospinal fluid higher than that of the blood within them; and Hill clearly regards it as axiomatic that normally the intracranial pressure can not be higher than the blood-pressure in the intracranial veins, or the cerebral circulation must cease. But it must be remembered that the intracranial sinuses are virtually channels in bone bridged across by dura, and can therefore withstand considerable pressure without collapse; and it seems illegitimate to assume, as Weed does, that the pressure in the narrow cerebral veins is as low as that in the broad intracranial sinuses

in the neighbourhood of the torcular. It is probably considerably higher, and it seems likely, therefore, that the pressure of the cerebro-spinal fluid, while higher than the venous pressure in the sinuses, is lower than that in the cerebral veins.

Hill investigated the effects of artificially increasing the intracranial pressure both by the injection of fluids under pressure and by the formation of localized foreign bodies. The effects are widely different according to the method which is used. As the fluid diffuses freely through the cranial cavity the rise in the intracranial pressure is general, and a gradual obliteration of the cerebral veins and capillaries takes place, until, when the injection pressure approaches the arterial pressure, the cerebral circulation ceases and death occurs with symptoms which are the same as those resulting from ligature of all the vessels supplying the brain. Hill was able to show that anæmia of the medulla was the factor responsible for death.

If, on the other hand, a localized foreign body be introduced, the cerebral vessels in its immediate neighbourhood are obliterated until the local pressure is equal to the arterial blood-pressure. Owing, however, to the viscosity of the brain substance and the resistance offered by the falx cerebri and the tentorium cerebelli, this increase of pressure is not readily transmitted from one compartment of the cranium to another. Hence, while a small foreign body introduced beneath the tentorium cerebelli may prove fatal by causing anæmia of the medulla, a much larger mass may be introduced, for example, in the frontal region, with but little effect on the intracranial pressure as a whole.

Hill also investigated the results of cerebral anæmia induced by ligature of the vessels supplying the brain, and his experiments have lately been elaborated by Winkin [12] who has found that a sharp rise of systemic blood-pressure, often reaching 200 mm. of Hg, occurs on occlusion of all the head arteries in cats, and that this rise of pressure is produced by vaso-constriction in the splanchnic area.

Tsubura [10] has recently demonstrated beyond doubt that this sharp rise of blood-pressure occurs if the intracranial pressure be raised by the injection of fluids; that it is due to vaso-constriction, the cardiac output being unchanged, and that it occurs after removal of the suprarenals. Cerebral hæmorrhage, the clinical equivalent of such experiments, also leads to a great rise in the blood-pressure. This rise of systemic blood-pressure, which results from a general increase in the intracranial pressure, must be interpreted as the response of the vasomotor centre to a progressive anæmia of the medulla.

There is evidence that the converse also occurs and that a lowering of the intracranial pressure below the tentorium cerebelli leads to a fall of the systemic blood-pressure. Thus, in three instances in cases in this series, tapping the cisterna magna during decompressive operations caused an immediate fall in the systolic blood-pressure of 15 mm. of Hg. In a fourth instance, a case of cystic tumour of one cerebellar hemisphere, the removal of bone in a suboccipital decompression was followed by marked bulging of the dura on the side of the tumour and the systolic blood-pressure was found to have fallen 20 mm. of Hg: tapping the cisterna magna in this case caused a further fall of 5 mm. of Hg. The best explanation of these facts would seem to be that the vasomotor centre responds to variations in the circulation through it, reacting to anæmia by raising and to an increased blood-flow by lowering the systemic blood-pressure.

With these facts in view, the blood-pressure was recorded in a number of cases of cerebral tumour in order to ascertain in what way, if any, it was affected by the increase in intracranial pressure due to the presence of a tumour. In twenty verified cases the average systolic pressure, previous to operation, was 115 mm. of Hg and the average diastolic pressure was 75 mm. of Hg. On comparing the figures obtained in cases of supratentorial tumour with those recorded in cases of subtentorial tumour it was found that the average in thirteen supratentorial tumours was: systolic 119 mm. of Hg and diastolic 76·3 mm. of Hg; while in seven subtentorial tumours the average was: systolic 110 mm. of Hg; and diastolic 74 mm. of Hg.

Thus, not only is the average blood-pressure in these cases subnormal, but it is lower in the case of subtentorial than supratentorial tumours. Moreover, the lowest figures recorded in supratentorial tumours were found in the cases showing evidence of the greatest intracranial pressure, both clinically and at operation. In No. 15, who had a glioma of the left temporal lobe, when admitted to hospital unconscious the blood-pressure was S.100/D.55; and in No. 55, with a cystic glioma of the left frontal lobe, when semi-conscious, it was S.105/D.80. In No. 7, who had a tuberculoma involving the frontal, parietal and temporal lobes on the right side, and so large as to cause a separation of the fronto-parietal suture of the skull and marked cranio-tabes superficial to it, the blood-pressure was S.88/D.60 and S.98/D.60 on two occasions at eleven days interval. While No. 20, a patient with a glioma of the pons which led to considerable internal hydrocephalus, had a blood-pressure of S.90/D.60 and S.95/D.60 mm. of Hg on dates separated by

an interval of three months, both before any operation had been performed. Fluctuations in the blood-pressure are common, and during temporary improvement in the symptoms a low pressure may rise to normal.

These figures form a striking contrast to the high pressures recorded during the intracranial injection of fluids and in cases of cerebral hæmorrhage. To account for this it must be remembered that the rise in intracranial pressure following the injection of fluid is sudden and general, while that resulting from a cerebral tumour is gradual and to a considerable extent localized by the falx cerebri and tentorium cerebelli to one compartment of the cranium. Thus the rise of pressure in the posterior fossa which results from a supratentorial tumour is probably comparatively slight. Tsubura has shown that slight rises in intracranial pressure induced by the injection of fluids cause a fall in blood-pressure owing to stimulation of the cardio-inhibitory centre. The bradycardia which is found in some cases of cerebral tumour suggests that the low blood-pressure may in these cases be due to the same cause. Tsubura also found that the intracranial injection of fluids did not lead to a rise in blood-pressure if the medullary centre had previously been destroyed by means of emboli. The subnormal blood-pressures found in cases of subtentorial tumour, especially tumours of the pons, may perhaps be due to the effect on the medullary centres of the local increase of pressure. The resulting medullary œdema and anæmia, though progressive, may be so gradual in its development as to lead to a depression of the vaso-constrictor centre without previously stimulating it. The tachycardia which is present in many patients with a subtentorial tumour can be explained as being due to a similar depression of the cardio-inhibitory centre.

Headache.

Of the three major symptoms of increased intracranial pressure—headache, vomiting and papillœdema—headache occurs in a larger proportion of cases of cerebral tumour than the other two. Of this series of sixty cases, headache was present in all except seven, i.e., in 88 per cent.

The headache of cerebral tumour possesses certain well-marked characteristics which are of diagnostic value. In the great majority of cases it is paroxysmal, the paroxysms varying from a few throbs of pain lasting seconds only, to attacks lasting from one to three hours. An hour is the duration most commonly mentioned by the patient. Con-

tinuous headache was not present from the first in any case in this series, but supervened in a small number of cases. It appears to be of grave prognosis. Neither rapid growth of the tumour nor the development of extreme internal hydrocephalus, as in Nos. 19, 23 and 26, was sufficient to cause the typical paroxysmal headache to become continuous.

The attacks occur with striking uniformity either on awakening in the early morning or during the night. Thus of thirty-three patients of whom inquiry was made as to the time when headache most often occurred, twenty stated that they awakened with headache in the early morning or during the night. In all cases it is liable also to be brought on by getting out of bed, by coughing, stooping, straining at stool, or violent exertion; and, in the case of tumours in the posterior fossa, by rotation of the head. Vomiting usually makes the headache worse; lying down relieves it and many patients become free from headache if strictly confined to bed. The intervals between the attacks vary in different cases. Sometimes two or three attacks occur during the day; in other cases the patient complains of headache only once a week. Most commonly the attack occurs on awakening and the patient is then free from pain for the rest of the day. The attacks increase in frequency as the tumour grows larger.

The character of the pain is variable. In some cases it is throbbing; usually it is described as a dull ache, or, as one patient put it, "a weighty pain." One patient, No. 31, who had two large cerebral aneurysms, one filled with clot, complained that straining at stool caused a sense of something bursting or opening and shutting in the head. The severity of the headache is often slight at first, but increases as the tumour grows and is much aggravated by the onset of hydrocephalus. The most severe and intolerable pain is that experienced if the headache becomes continuous. Soreness of the scalp is sometimes experienced when the headache is severe, more commonly when the tumour is in the frontal lobe or the pituitary gland than with tumours elsewhere; in these cases the soreness is frequently in the distribution of the first division of the fifth cranial nerve.

The stage of the illness at which the patient first complained of headache was found to vary widely in different cases. Whether it is an early or late symptom appears to be determined partly by the site of the tumour and partly by its rate of growth. For the purpose of this investigation the terms "early," "intermediate" or "late" have been used according as a symptom has developed during the first, middle or

terminal one-third of the duration of the disease, calculated from the date of the development of the first symptom to the date of operation or death if no operation was performed. Estimated in this way headache was found to occur early in forty-one out of the fifty-three cases in which it occurred.

The following table of verified cases shows the influence of the site of the tumour on the stage at which headache begins.

TABLE I.—SHOWING STAGE OF ONSET OF HEADACHE IN RELATION TO SITE OF TUMOUR.

Site of tumour	No. of cases	Early	Intermediate	Late	Absent
Frontal	9	6	—	—	3
Fronto-parietal	5	4	—	1	—
Parietal	2	—	—	1	1
Temporal	5	5	—	—	—
Occipital	1	1	—	—	—
3rd ventricle	1	1	—	—	—
Pons	3	2	—	—	1
4th ventricle	1	1	—	—	—
Cerebellum	6	5	—	—	1
8th nerve (bilateral) ..	1	—	1	—	—
Multiple	1	1	—	—	—

It will be seen that headache was late or absent in six out of sixteen cases of tumours involving the frontal or parietal lobes and in one case each of pontine and cerebellar tumour; while it was early in the remainder of cases in which the pons and cerebellum were involved, and in all cases of tumours of the temporal lobe and ventricles. Clearly tumours of the frontal and parietal lobes can attain a larger size than tumours situated in the temporal or posterior fossæ of the skull before they cause the same degree of tension on the meninges. Subtentorial tumours, moreover, and tumours of the ventricles, give rise to internal hydrocephalus early, and this is doubtless another factor in the early causation of headaches in these cases.

The influence of the rate of growth of the tumour on the stage at which headache occurs is revealed by estimating the average duration of the disease in cases in the same site grouped according to the stage at which headache began. This has been done for frontal and parietal tumours which are grouped together, since the distinction between them is arbitary, and subcortical tumours frequently involve both lobes.

TABLE II.—FRONTAL AND PARIETAL TUMOURS.

Stage of onset of headache	No. of cases	Average duration of disease in months
Early	10	9
Late	2	31
Absent	4	50

It is obvious that a slowly growing tumour will take longer to attain a sufficient size to cause headache than a neoplasm of more rapid growth, but there is some evidence that the more gradual the increase of pressure the larger the size a growth may attain before it gives rise to headache. Whether the tumour grows mainly by expansion or mainly by infiltration is also of importance : since an infiltrating neoplasm may effect the destruction of a considerable amount of brain tissue with only a minimal increase in bulk and hence only a slight increase in the local intracranial pressure.

Having considered the characteristics of the headache due to a cerebral tumour we are in a position to attempt to account for them before investigating the localizing value of the symptom.

It has been proved that the brain itself and the leptomeninges are insensitive to pain ; it seems likely, therefore, that the headache is due to the abnormal tension of the dura which results from the pressure of the tumour, and possibly to pressure upon the bones of the skull. This view is supported by the relief afforded by decompression and incision of the dura.

But though there is abundant evidence that a large tumour exerts a constant pressure above the normal upon the dura, yet the headache is paroxysmal. It is not uncommon to find at operation evidence of greatly increased intracranial pressure in the neighbourhood of the tumour in a patient whose headaches have been brief and paroxysmal, or who has actually been free from headache for weeks. No 7 had a large tuberculoma which involved the right frontal, temporal and parietal lobes and caused marked cranio-tabes, bulging of the skull superficial to it and separation of the fronto-parietal suture. Yet this patient's headaches occurred at intervals of several days and lasted only about half an hour.

Clearly, the dura can be subjected to a constant tension much above the normal without headache resulting. The circumstances which

induce the headache suggest an explanation of its paroxysmal character. Thus stooping, coughing, vomiting and straining at stool, cause an obstruction to the free outflow of blood from the veins of the neck and hence from the intracranial sinuses. Exertion causes a rise in the arterial blood-pressure, and MacWilliam [6] quotes various authorities to the effect that the systolic blood-pressure falls during sleep from 15 to 30 mm. of Hg in normal persons; and rises again during the later part of the night and on awakening. All the acts which induce headache are therefore associated with a rise in the blood-pressure and hence in the intracranial pressure; normally the resultant increased tension of the dura is equal at all points and transitory since the rise of intracranial pressure can be compensated for by the passage of cerebrospinal fluid from the cranium to the spinal theca. Superficial to a tumour, however, which is in effect a foreign body embedded in the brain, the dura is subjected to a tension greater than that elsewhere, and the presence of the abnormal mass, especially if it lead to hydrocephalus, interferes with the normal compensatory mechanism and prolongs the abnormal pressure. The dura, which can adapt itself to a gradual increase in tension, is sensitive to rapidly induced, albeit transitory, increases. Hence we can understand the paroxysmal nature of the headache, its relation to awakening and to such acts as cause a rise of blood-pressure, and its relief by confinement to bed and by the incision of the dura during decompression.

The value of the distribution of the headache as an indication of the site of the tumour is disappointingly slight. For this there are several reasons. The increased intracranial pressure resulting from a tumour of any size is not itself localized but is more or less diffused throughout the compartment of the cranium in which the tumour lies; and the patient's power of attention is frequently dulled and his memory impaired, so that his answers to questions are vague.

It will be convenient to consider supratentorial and subtentorial tumours separately. There were twenty patients with verified unilateral supratentorial tumours who suffered from headache and were able to describe its distribution. Of these the headache was confined to the side of the tumour in seven, predominated on the side of the tumour in four, and was bilateral in nine. Thus, in eleven out of twenty, the headache was confined to, or predominated upon, the side of the tumour. It does not appear to be of value for more accurate localization. Nor is headache in cases of subtentorial tumour of much value for localizing purposes. For while a tumour remains small it

does not cause headache; and before it becomes very large it gives rise to hydrocephalus with a characteristic clinical picture to be considered later. Two cases, Nos. 27 and 29, both with tumours near the cerebello-pontine angle, complained of headache with a distribution which Cushing [1] describes as typical of the early stage of these tumours. This headache is a sharp pain radiating from the occiput to the mastoid process on the same side as the tumour and sometimes reaching as far forward as the frontal region. The remainder, with the exception of Nos. 22 and 24, who were free from headache, described a type of headache which seems to be symptomatic of internal hydrocephalus, beginning in the occiput and radiating over the vertex to the brow.

Tenderness of the skull on percussion, though a much less common sign of cerebral tumour than headache, is probably a more reliable indication of the site of the tumour.

Vomiting.

Vomiting occurs in a smaller proportion of cases of cerebral tumour than does headache; it was present in thirty-nine out of the sixty cases in this series, or 65 per cent. Like headache it occurs characteristically in the early morning or during the night. Of thirty patients who were asked whether they vomited at one time of day more than another, twenty-three described early morning attacks and two nocturnal attacks. The time of the morning attacks varies from 6 a.m. to 10 a.m. Most patients vomit immediately on awakening or on getting out of bed; a smaller number as a result of taking breakfast or a cup of tea. The frequency of the vomiting varies widely in different patients and according to the stage of the disease. At first vomiting may occur at intervals of weeks or days; later the patient vomits every morning, and finally in the absence of operative interference vomiting may occur many times a day and the patient be able to retain very little food. Some patients from the beginning are subject to bouts of vomiting of this character lasting two or three days, and occurring at intervals of several weeks during which they are free from the symptom.

Vomiting that is cerebral in origin is often said to be characterized by an absence of warning or nausea, but this is by no means always the case. Of twenty-two patients who complained of vomiting and of whom inquiry was made, eight only said that they had no warning, four that they had "little" or "not much" warning, while ten, on the other hand, complained of severe nausea or retching.

Whether or not vomiting occurs, and the stage of the disease at

which it does so, appears to be only indirectly influenced by the site of the tumour. The following table shows the verified cases classified according to the site of the tumour, and the stage at which vomiting developed in the cases in each class.

TABLE III.—SHOWING STAGE OF ONSET OF VOMITING IN RELATION TO SITE OF TUMOUR. CASES CLASSIFIED AS "EARLY," "INTERMEDIATE," AND "LATE" ACCORDING AS VOMITING BEGAN DURING THE FIRST, INTERMEDIATE OR TERMINAL ONE-THIRD OF THE DURATION OF THE DISEASE.

Site	Number	Early	Intermediate	Late	Absent
Frontal	9	2	—	1	6
Fronto-parietal ..	6	3	1	—	2
Parietal	2	—	—	1	1
Temporal	5	1	—	2	2
Occipital	1	1	—	—	—
3rd ventricle	1	1	—	—	—
4th ventricle	1	1	—	—	—
Pons	3	1	—	1	1
Cerebellum	6	6	—	—	—
8th nerve	1	—	—	—	1
Multiple	1	1	—	—	—

From this it will be seen that vomiting was absent in six out of nine frontal tumours, but in only three out of eight tumours involving the parietal lobe, and two out of five involving the temporal lobe; while only two out of twelve patients with subtentorial tumours were free from vomiting.

This raises the interesting question of the ætiology of the vomiting. The first hypothesis considered was that it might be due to pressure upon the vomiting centre in the medulla, but this had to be rejected when it was found that vomiting was absent in one case of pontine tumour, No. 21, and only occurred on one occasion in another, No. 22; while it was an early symptom in all five patients with cerebellar tumours, and in five cases of tumour of the frontal or parietal lobes. For similar reasons, vomiting could not be attributed to irritation by pressure of the afferent fibres of the vagus. No. 29, who had bilateral eighth nerve tumours with direct compression of the left vagus, did not vomit; while No. 18, with a tumour in the left occipital pole, vomited early in the illness.

Then the relationship between hydrocephalus and vomiting was noted and it was found that in no case was vomiting present in the absence of hydrocephalus; while the degree of hydrocephalus present was roughly proportional to the length of time that had elapsed between the onset of vomiting and death. This is shown in Table IV.

TABLE IV.—SHOWING RELATION OF THE STAGE OF ONSET OF VOMITING TO THE DEGREE OF HYDROCEPHALUS FOUND AT AUTOPSY.

No. of case	Site of tumour	Stage at which vomiting began	Survival period after onset of vomiting in weeks	Degree of hydrocephalus at autopsy
54	Frontal	Late	1	Slight
52	Parietal	Absent .. .	—	Absent
13	Temporal	Late	7	Considerable
15	Temporal	Late	3	Moderate
17	Temporal	Absent	—	Slight
19	3rd ventricle ..	Early	208	Extreme
20	Pons	Early	18	Considerable
21	Pons	Absent	—	Absent
22	Pons	Late (once only) ..	2	Slight
23	4th ventricle ..	Early	104	Great
24	Cerebellum ..	Early	11	Moderate
26	Cerebellum ..	Early	52	Great
58	Cerebellum ..	Early	4	Considerable
29	Bilateral 8th nerve	Absent	—	Absent

The number of cases which throw light on this point is necessarily small because in many cases decompression and the resultant hernia cerebri make it difficult to draw any reliable conclusion as to the previous presence of hydrocephalus.

Two of the cases in Table IV are worthy of consideration in more detail. In No. 19 a polypoid glioma, 0·5 cm. long and 0·2 cm. in diameter, growing from the posterior commissure into the third ventricle, by obstructing the anterior aperture of the aqueduct of Sylvius gave rise to an extreme degree of hydrocephalus of the lateral and third ventricles of four years' duration. This patient vomited throughout her illness, and it seems impossible to attribute the vomiting to anything but the hydrocephalus. No. 29, the duration of whose illness was twenty-seven months, was found at autopsy to have multiple small dural endotheliomata; large neuromata (5 by 4 by 4 cm. and 3·5 by 2·5 by 2·5 cm.) on each eighth nerve; and a carcinomatous condition of the choroid plexuses of the lateral and third ventricles. In this case, in spite of two subtentorial tumours producing lateral compression of the pons, there was no hydrocephalus, presumably because the degenerate condition of the choroid plexus led to a greatly diminished secretion of cerebrospinal fluid. Vomiting did not occur.

To sum up, we find that in the absence of hydrocephalus vomiting does not occur however close to the medulla the tumour may lie; that hydrocephalus alone is sufficient to cause vomiting, and that the degree of hydrocephalus found at autopsy is roughly proportional to the length of time that has elapsed since the onset of vomiting. It should be

noted that the degree of dilatation of the ventricles found at autopsy is not necessarily an accurate index of the extent to which the intraventricular tension was raised during life, since the presence of a large supratentorial tumour may limit the capacity of the ventricles to expand in spite of a raised intraventricular tension. Vomiting in cases of cerebral tumour appears to be a reflex act of which the appropriate stimulus is a rise in intraventricular tension.

The Ætiology and Symptoms of Hydrocephalus in Cases of Cerebral Tumour.

At this point it will be convenient to consider in what way a cerebral tumour may cause internal hydrocephalus, and what are the indications of its onset.

A tumour obstructing one foramen of Monro will lead to a hydrocephalus confined to one lateral ventricle; but this is a rare condition, and such a case did not occur in this series. Usually the lateral and third ventricles are distended, but not the fourth ventricle, except in the case of tumours of this ventricle itself. The obstruction, therefore, lies in the course of the aqueduct of Sylvius. There are two possible causes of such a hydrocephalus. The pressure of a tumour might lead to an absolute obstruction of the aqueduct. On the other hand, pressure upon the vein of Galen might lead to an excessive secretion of cerebrospinal fluid, resulting in a relative obstruction if the aqueduct of Sylvius were too small to allow of its escape at the same rate as its secretion. This, according to Dandy [2], is a very rare cause of hydrocephalus; while the frequency with which actual distortion of the brain-stem is found at autopsy suggests that true obstruction frequently occurs. The aqueduct of Sylvius is clearly the most vulnerable part of the cerebrospinal drainage system. Here the channel is narrowest and most readily obstructed, while displacement of the mid-brain is resisted by the sharp unyielding edge of the tentorium cerebelli. Examination of a normal brain shows how readily displacement of one hemisphere of the cerebellum or of the temporal lobe on one side produces torsion of the mid-brain and obstruction of the aqueduct. Probably the mechanical effect on the mid-brain of tumours in these situations is a combination of displacement and torsion.

The suggestion that vomiting in cases of cerebral tumour is always a symptom of hydrocephalus finds confirmation in the ready explanation which this theory offers of the incidence and characteristics of the vomiting. Thus vomiting is rare in the case of frontal tumours because

tumours in the frontal lobe rarely produce hydrocephalus, since they must attain a large size before they can cause displacement of the brain-stem. Cerebellar tumours and tumours of the ventricles cause hydrocephalus early, and vomiting was in all such cases in this series one of the first symptoms complained of. It has been shown that in the case of pontine tumours vomiting does not occur in the absence of hydrocephalus; and tumours of the pons may prove fatal before they cause hydrocephalus.

The characteristics of the vomiting in cases of cerebral tumour can also be explained by its relation to hydrocephalus. It has been shown that a rise of intracranial pressure occurs on awakening, and that in patients suffering from a cerebral tumour it is likely to be abnormally great in the neighbourhood of the tumour and unduly prolonged. It is probable that transitory attacks of hydrocephalus occur at such times owing to a temporary obstruction to the aqueduct of Sylvius. On the other hand, when hydrocephalus is established, such rise of intracranial tension must cause a rise of intraventricular tension, and this appears to be the cause of the vomiting.

The signs and symptoms of hydrocephalus are well illustrated by several cases in this series, especially by No. 19, in whom, as has been explained already, symptoms extending over a period of four years were attributable entirely to the internal hydrocephalus.

The headache characteristically radiates from the occipital region over the vertex to the brow, and otherwise conforms to the type of headache caused by a cerebral tumour. Vomiting is an earlier indication of hydrocephalus than either headache or papillœdema, which may both be absent if the hydrocephalus is slight as in No. 24. In No. 20, a case of tumour of the pons, papillœdema did not develop until eight weeks after the onset of vomiting. Severe papillœdema followed by consecutive optic atrophy and gross visual impairment is not uncommon. Attacks of vertigo, syncope or actual convulsions may occur; mental deterioration and irritability of temper are common, and dysphasia was present in No. 19. Cranial nerve palsies are often present, the sixth being most often affected; and deafness and tinnitus may be complained of. Involvement of the pyramidal tracts is indicated by weakness and spasticity and bilateral extensor plantar responses. Long-standing hydrocephalus occurring early in life leads to expansion and thinning of the bony cranium with well marked trabeculation, so that the radiographic appearance of the calvarium is that of beaten silver. Finally, the distension of the thinned floor of the third ventricle results in

flattening of the sella turcica—easily recognized in radiograms—and pressure atrophy of the pituitary gland. This occurred in two cases, Nos. 19 and 26, both of whom showed adiposity and infantilism of the Fröhlich type.

The severity of the symptoms of hydrocephalus appears to depend largely on the acuteness of its development. Nos. 19 and 23, cases of tumour of the third and fourth ventricles respectively, in whom symptoms of hydrocephalus had been present for four and two years, showed less profound mental disturbance than No. 58, who was drowsy and hard to rouse, and at times disorientated, although his symptoms, due to a secondary tumour of the right lobe of the cerebellum, had been present a month only and the dilatation of the ventricles found at autopsy was much less extreme than in the other two cases.

Cerebral Œdema as a Complication of Cerebral Tumour.

The development of œdema in the cerebral tissue around a tumour may contribute largely to the increase in intracranial pressure, and may with advantage be considered at this point. Such œdema may develop and spread with great rapidity and is often responsible for the sudden onset of coma in unoperated cases; or, on the other hand, its progress may be extremely slow, and the signs and symptoms to which it gives rise may be attributed entirely to the tumour itself. The œdema is probably due to venous obstruction produced by the tumour in its neighbourhood; and owing to the rigidity of the cranium no means exists by which the cerebral tissue can swell and relieve the circulation of this embarrassment. The same conditions operate in maintaining the local œdema of cerebral contusions, and Trotter [9] states that four years after an injury he has found in a contused area of brain all the signs of an injury only a few weeks old.

Two cases in this series well illustrate the varying effects of cerebral œdema. No. 1, who was found to have gliomata involving both frontal lobes, suddenly became unconscious after suffering for several days from continuous headache, persistent vomiting and drowsiness. Decompression, first on the right side and then on the left, was followed by temporary recovery of consciousness on each occasion, but the patient died in coma sixteen days after he first lost consciousness. At autopsy the greater part of both frontal and parietal lobes was found to be œdematous.

No. 6 began in 1919 to suffer from Jacksonian convulsions which began in the left side of the face, and were not associated with headache

or vomiting. In 1921, as the fits were becoming more frequent, a right subtemporal decompression was performed. After this the fits continued but without loss of consciousness: and he began to suffer from severe headache and vomiting. By 1923 he had developed in addition a left hemiplegia and bilateral papillœdema, and there was a large hernia cerebri at the site of the decompression. A left subtemporal decompression was, therefore, performed which afforded temporary relief from headache but was followed by severe aphasia and a right hemiparesis. In a few months the headaches returned and became almost intolerable. He became completely blind and died six months after the second operation with a large hernia cerebri on each side. The tumour found at autopsy was a glioma 3 cm. in diameter occupying the lower part of the right precentral convolution: but there was widespread œdema of both cerebral hemispheres.

In this case the first decompression must have caused vascular changes which led to a slowly progressive cerebral œdema to which all the symptoms of increased intracranial pressure were due.

Papillœdema.

Our knowledge of the pathology of papillœdema is due to a number of workers, especially to Deyl [3], Dupuy-Dutemps [4] and Holmes and Paton [7]. These last authors reached the conclusion that it is "in the first place due to the venous engorgement that results from the rise of intravenous pressure that is necessary in order that circulation should be maintained in the intravaginal portion of the vein where this is subjected to an increased sheath pressure. The increased sheath pressure is also the origin of the second factor, the obstruction to the lymph drainage from the papilla."

In this series of sixty cases of cerebral tumour papillœdema or secondary optic atrophy was present in forty-five, or 75 per cent. Primary optic atrophy was present in two cases, both pituitary tumours: while in thirteen cases the fundi were normal. The proportion with normal fundi is thus 21·6 per cent., a figure almost the same as that noted by Paton in his series of two hundred cases.

The relation of the site of the tumour to the incidence of papillœdema was investigated by Paton [8], who found that subcortical and pontine tumours showed the highest incidence of cases without papillœdema, about 40 per cent. in each situation, while this symptom was present without exception in all tumours of the temporo-sphenoidal lobe, cerebellum and fourth ventricle, the incidence in other situations lying

between these extremes. Pontine tumours appear never to give rise to papillœdema as long as the tumour is confined to the pons. Similarly the severity of the papillœdema is greatest in cerebellar and extracerebellar tumours, and tumours of the thalamus and mid-brain; least in subcortical and postcentral tumours; while frontal and temporosphenoidal tumours and tumours of the ventricles themselves give rise to a papillœdema which is intermediate in severity. Paton offers no explanation for these variations in incidence and severity except that they are correlated with variations in the intracranial pressure found at operation.

If the incidence and stage of onset of papillœdema be compared with the incidence and stage of onset of vomiting, it is found possible to divide the cases with papillœdema into two groups. Only those cases are of value in this connection in which the time of onset of vomiting could be accurately ascertained and in which papillœdema developed while the patient was under observation. It was found that in all such cases of tumours of the frontal, parietal and temporal lobes, either papillœdema was present without vomiting or it preceded the onset of vomiting by weeks or months. In the case of subtentorial tumours, on the other hand, vomiting preceded papillœdema. If the contention already advanced be accepted, viz., that vomiting is always the result of hydrocephalus, it would appear probable that in the case of all subtentorial tumours and also in the case of tumours in certain other situations—viz., the ventricles, mid-brain and occipital lobes—the papillœdema is due to the rise of intracranial pressure which results from the hydrocephalus. While in the case of tumours of the frontal, parietal and temporal lobes it is caused by the local rise of intracranial pressure produced by the tumour itself. The following table shows how closely in the case of subtentorial tumours the presence of hydrocephalus and papillœdema are correlated.

Of special interest in this connection is No. 29, already described in the section on vomiting. This patient was found to have a large fibroneuroma of each eighth cranial nerve, causing distortion of the pons and considerable increase in the mass of the structures in the posterior fossa. There were also present in this case multiple small dural endotheliomata and a carcinomatous condition of the choroid plexuses of the lateral and third ventricles. Probably owing to this last abnormality there was not a secretion of cerebrospinal fluid sufficient to cause internal hydrocephalus in spite of obstruction to the aqueduct of Sylvius, and the patient suffered from neither vomiting nor papillœdema. This case

strongly confirms the view that subtentorial tumours give rise to papillœdema only indirectly by causing hydrocephalus.

TABLE V.—SHOWING RELATION OF PAPILLŒDEMA TO PRESENCE OF HYDROCEPHALUS IN VENTRICULAR AND SUBTENTORIAL TUMOURS.

No.	Site	Degree of hydrocephalus	Papillœdema present or absent	Severity of papillœdema
19	3rd ventricle ..	Extreme	Present	Marked secondary optic atrophy
20	Pons	Considerable ..	Present	Swelling + 2D.
21	Pons	Absent	Absent	—
22	Pons	Slight	Absent	—
23	4th ventricle ..	Great	Present	Secondary optic atrophy
24	Vermis of cerebellum	Moderate ..	Absent	—
26	Cerebellum ..	Great	Present	Secondary optic atrophy
58	Cerebellum ..	Considerable ..	Present	Swelling + 2D.
29	Bilateral 8th nerve	Absent	Absent	—

Thus, in patients suffering from cerebral tumour papillœdema may arise in either of two ways. The raised pressure in the optic sheaths may be due to the comparatively localized rise in intracranial pressure in the neighbourhood of the tumour itself On the other hand, the rise of intracranial pressure which leads to papillœdema may be the result of the internal hydrocephalus caused by a tumour quite remote from the optic nerves. The recognition of the alternative modes of origin of papillœdema affords an explanation of the apparent anomalies noted by Paton in the incidence and severity of this sign in relation to the site of the tumour. Thus 40 per cent. of the patients with pontine tumours escape papillœdema because, as shown in Table V, hydrocephalus may develop late in such cases compared with the striking neurological signs which bring the patient under observation early. Papillœdema of the greatest severity appears to be caused by hydrocephalus of comparatively acute onset such as results from cerebellar and extracerebellar tumours, which cause obstruction to the aqueduct of Sylvius. Tumours of the third and fourth ventricles give rise to a hydrocephalus of much more gradual onset and the papillœdema in these cases is of moderate severity only.

In the other group of cases papillœdema is due to the increased pressure within the optic sheaths which results from the local rise in intracranial pressure due to the tumour. In this group, as might be expected, papillœdema is most constant and most severe in the case of tumours of the frontal and temporal lobes, i.e., those situations nearest to the optic nerve; while when the tumour is more remotely situated,

in the parietal lobe, or is subcortical, this sign is less frequent and, when it occurs, less marked.

In the only case of occipital tumour in this series, No. 18, the papillœdema was of great severity with 6D. of swelling of each disc and was probably hydrocephalic in origin.

Paton has noted that the degree of loss of vision in patients with cerebral tumours is often apparently not proportional to the severity of the papillœdema. This he explains by attributing the loss of vision in some cases to the pressure upon the optic chiasma of the floor of third ventricle distended by internal hydrocephalus. In this series, however, the visual loss has not been the greatest in those cases in which the hydrocephalus has been most severe, e.g., Nos. 19, 23 and 26; though in all these cases the dilatation of the ventricles was of long standing, viz., four years, two years and one year, and in both Nos. 19 and 26 the distended floor of the third ventricle had produced great flattening of the sella turcica and hypopituitarism. Complete blindness, on the other hand, occurred in Nos. 7, 18, 25 and 27 within an average of six months from the onset of the illness. The extent of the visual loss would seem therefore to depend upon the acuteness with which the papillœdema develops, a rapidly developing œdema proving more destructive to the fibres of the optic nerve than a gradually progressive one.

The Localizing Value of the Signs of Increased Intracranial Pressure.

In a certain number of cases of cerebral tumour the focal signs are either too slight or too conflicting to be of value for accurate and early localization. This investigation was undertaken in the hope that an analysis of the signs of increased intracranial pressure might yield data of localizing value in such cases. Headache, vomiting and papillœdema have long been described as the classical signs of a cerebral tumour; but they are not equally constant. Headache was present in 88 per cent., papillœdema in 75 per cent. and vomiting in 65 per cent. of the cases in this series. The number of cases in which all three signs were present amounted to only 60 per cent. of the total. Headache has been found to be of small value in localization, though the occurrence of a headache confined to, or predominating upon, one side of the head strongly suggests a tumour on that side. Two types of headache have been recognized to have special significance. Pain arising in the occipital region on one side and radiating through the base of the mastoid process to the frontal region on the same side is usually due to

a tumour in the posterior fossa on that side. While pain arising in the occipital region and radiating over the vertex to the brow is suggestive of the onset of internal hydrocephalus.

Of much greater value in localization is the time of onset of vomiting, especially when considered in relation to the time of onset of papillœdema. Vomiting, it is contended, is always a symptom of hydrocephalus; and this fact explains the relationship between its time of onset and the site of the tumour. Tumours in certain situations give rise to hydrocephalus early; tumours in other situations much later, or not at all. In the first group must be placed tumours of the third and fourth ventricles, of the cerebellum, and the one case of occipital tumour which occurred in this series: in the second group tumours of the frontal, parietal and temporo-sphenoidal lobes. In tumours of the pons hydrocephalus sometimes occurs early but is sometimes late or absent.

In every case of tumour in the first group in this series the occurrence of vomiting coincided with the beginning of the illness and was one of the first symptoms of which the patient complained. In only one-quarter of the cases in the second group did vomiting occur during the first one-third of the duration of the illness, while in half the cases it was absent throughout. Further, of the few cases in which it occurred comparatively early, in none was it among the first symptoms complained of, being always preceded by focal signs.

The stage of onset of papillœdema is another point of distinction between the two groups. In the first group and in tumours of the pons, papillœdema is due to hydrocephalus, in the second group to the local rise in intracranial pressure resulting from the tumour. In the first group, if the patient comes under observation sufficiently early, vomiting is found to precede papillœdema; being apparently the earlier sign of hydrocephalus. In no case has the reverse been found to occur. In the second group papillœdema precedes vomiting, since with tumours of the frontal, parietal and temporo-sphenoidal lobes the rise in intracranial pressure usually causes a rise in the pressure within the optic sheaths earlier than it leads to obstruction of the aqueduct of Sylvius.

The average blood-pressure has been found to be subnormal in patients with a cerebral tumour, and to be lowest in patients with subtentorial or very large supratentorial tumours.

I am indebted to the staff of the London Hospital and the Hospital for Epilepsy and Paralysis, Maida Vale, for permission to examine their patients, and especially to Dr. George Riddoch, who

suggested to me the subject of this investigation, for constant help and kindly criticism. My thanks are also due to Professor Turnbull and to Dr. Douglas McAlpine for reports on the results of autopsy in a number of cases.

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Proceedings of the Section of Neurology of the Royal Society of Medicine.

President—Dr. E. Farquhar Buzzard.

Clinical Meeting held at the West End Hospital for Nervous Diseases, Welbeck Street, W. 1, on December 11, 1924.

A Case of Syringo-bulbo-myelia with Unilateral Nerve-deafness and Immobility of the Opposite Vocal Cord.

By Sir James Dundas-Grant.

Patient, a man aged 46, referred to the Throat and Ear Department of the West End Hospital for Nervous Diseases, in 1922, with right-sided deafness and a change in the character of the voice. The deafness, as proved by the tuning-fork tests, was of the "nerve" type, but the relative loss of hearing for the highest-pitched tones (Galton's whistle) was not so marked as in the more typical cochlear diseases, such as syphilis. Bárány's caloric test (carried out by means of cold air) showed loss of reaction (nystagmus, past-pointing and falling), and this was also the case with the galvanic (Babinsky) reaction, showing that the disease was situated more deeply than the internal ear—probably in the acoustic nucleus. The reactions on the left side were normal to both tests. There was complete paralysis of the left vocal cord, while the palate was so paretic on both sides that hemiplegia of the velum, though probably present, could not be distinguished.

Dr. Worster-Drought stated that the onset of the condition occurred during 1917, with numbness of the fingers, while about a year later weakness and wasting of the hands appeared. Results of physical examination: Pupils equal and reacting to light; fundi normal; tongue deviates to the left on protrusion. Bilateral atrophy and weakness of the intrinsic muscles of the hands; arm muscles generally atrophic with occasional fibrillary tremors. Abdominal reflexes absent: knee- and ankle-jerks exaggerated; plantar reflexes extensor. An area of anæsthesia to pain and thermal stimuli extends upwards from the sixth thoracic segment, involving both arms, reaching posteriorly to above the occiput and anteriorly to the level of the lower lip.

Sir James Dundas-Grant commended to the neurologist the apparatus devised by himself for the application of cold air to the ear for carrying out the labyrinthine tests, as free from the inconvenience and danger attending the use of cold water for the purpose. He demonstrated its use in the case under consideration.

A Case of Dyspituitarism following Encephalitis Lethargica.

By Dr. C. WORSTER-DROUGHT.

J. M., aged 14. In December, 1921, he developed severe headache and giddiness, and was admitted to hospital suffering from encephalitis lethargica. He remained "unconscious" for thirty-three days and was in hospital for three months. Since his convalescence he has gradually increased in bulk, and has been most difficult to manage, his disposition having completely altered. There is no family history of significance.

His present symptoms include excessive adiposity, vague pains in the limbs and body, frequent vertical headaches, restlessness and irritability, lack of mental concentration and frequency of micturition.

Physical signs.—He exhibits pronounced general obesity with broad hips and well-developed breasts, smooth, soft skin and early pubic hair. The testicles and external genitalia are normal. His height is 5 ft. 3½ in., and weight 13 st. Muscular power relatively weak. Circumference measurements of limbs: upper arms, 12 in.; forearm, 10 in.; thigh, 21½ in.; and calf, 16 in. His temperature is invariably subnormal, never reaching above 98° F.; the heart, lungs, and abdominal viscera show nothing abnormal, the pulse-rate averages 72, and the blood-pressure is 110 mm. Hg systolic and 75 mm. diastolic. The urine shows no abnormality. Central nervous system: the pupils are equal and react normally; visual fields and optic discs are also normal. The abdominal reflexes are brisk and equal, knee- and ankle-jerks normal and the plantar reflexes flexor. There is no disorder of sensation or co-ordination. The cerebrospinal fluid contains only five lymphocytes per cubic millimetre, with a normal protein content and negative Wassermann and colloidal gold reactions. The blood contains 5,750,000 red cells per cubic millimetre, with a general reduction in size of the corpuscles and moderate anisocytosis. The hæmoglobin is 86 per cent. and the colour index 0·75. The white cells show both an absolute and a relative lymphocytosis, viz., 10,600 cells per cubic millimetre, with 47 polymorphonuclears, 50 small lymphocytes, 0·5 large mononuclear and 2 eosinophils per cent. X-ray examination reveals no abnormality of the sella turcica. Sugar tolerance is increased, no glycosuria following the ingestion of 300 grm. of dextrose. The resting blood-sugar is 0·11 per cent. The blood-sugar curve—following the oral administration of 50 grm. of glucose—is abnormal in that (1) the apex is not reached for one and a half hours (as compared with half an hour in the normal subject); (2) the altitude is abnormal, reaching only 0·14 per cent. (normal 0·17 per cent.); and (3) the blood-sugar does not regain the normal level within two hours. Mentally, the boy is bright and intelligent, but extremely difficult to control. He is wayward and irritable, lacks discrimination between right and wrong, and loses his temper upon very slight provocation. A headache renders him violently hysterical. For any offence he expresses great sorrow and repentance; in spite of protestations to the contrary the offence is repeated. It has been impossible to retain him in hospital owing to him not being amenable to

the slightest discipline. His relatives state that his disposition was very good preceding his illness, and that he never gave any trouble whatever.

Dr. WORSTER-DROUGHT said that the general adiposity, normal genitalia, relative lymphocytosis, increased sugar tolerance and blood-sugar curve suggested a dyspituitarism of the Dercum type rather than of the Frölich type. Both types had been ascribed to decreased function on the part of the posterior lobe of the pituitary gland; had the condition developed at an earlier age in this patient, the dyspituitarism would probably have been identical with the Fröhlich form. Since Camus and Roussy had shown that typical dyspituitary syndromes could be produced in dogs by comparatively slight injury to the base of the brain, above but not involving the pituitary gland, it was interesting to speculate how far the condition in this case might be due to involvement by the encephalitic process of the nuclei of the tuber cinereum, rather than of the posterior lobe of the pituitary gland itself.

Congenital Bilateral Athetosis.

By Dr. C. WORSTER-DROUGHT.

E. B., aged 11, presents generalized, involuntary and irregular movements which have existed since birth.

She is the eighth of ten children. One sister, now aged 26, is quite normal, but the other eight children all died with jaundice between the ages of three days and four weeks; of these latter only one was premature. The patient was born at full term, labour being normal. She walked at $5\frac{1}{2}$ years, but has never talked.

The generalized movements are irregular, jerky and wriggling, and are most pronounced in the face, neck and upper limbs. The face is constantly grimacing and the tongue and soft palate are also affected. The movements are increased by emotion, but tend to subside on purposeful movements, e.g., she can raise with one hand and drink a glassful of water without spilling any. The lower limbs are only slightly affected. She is able to walk without assistance in a somewhat ataxic fashion, the gait being punctuated at frequent intervals with asymmetrical jerky movements of the legs. In walking she tends to deviate either to the right or left from a straight line. There is no spasticity, muscle tone being normal; the knee and ankle-jerks are brisk and equal. The abdominal reflexes are present and equal, plantar reflexes flexor, and sphincters normal. The Wassermann reaction is negative both in blood and cerebro-spinal fluid, the latter being normal in all respects.

She has never been to school and can neither read, write, nor dress herself, but in her habits she is quite clean. Although unable to articulate, she can phonate, the only recognizable word being "more." From time to time she emits a sound resembling "ah wah!" She understands most things said to her, and when her attention is obtained she will carry out correctly simple commands, such as "Eva, get out of bed!" or "Strike a match!" &c. If the command does not interest her very much it has to be repeated several

times before she will obey, e.g., "Touch your nose!" "Clap your hands!" &c. If asked to imitate movements, she does so quickly and correctly.

Dr. WORSTER-DROUGHT said that the congenital athetosis was termed "congenital, bilateral athetosis," owing to the lack of a more suitable name. Although grimacing was present the movements of the limbs were more choreic than athetoid. The condition was that particular type of so-called "cerebral diplegia," in which the agenesis affected the corpus striatum, in all probability the putamen and caudate nucleus particularly.

An Unusual Case of Myopathy.

By Dr. C. WORSTER-DROUGHT.

J. U., male, aged 48, complains of "wasting and weakness of the thigh muscles and weakness of the back." The condition developed in 1917, when he began to complain of some pain and weakness in both legs from the thighs to the feet. Since that time the thigh muscles have gradually atrophied. Weakness of the back has been noticed since 1919. There is no family history nor previous illness of significance.

Physical signs.—The pupils are equal and react normally. There is some temporal and malar hollowing, but all cranial nerves are otherwise normal. There is some lordosis and slight scoliosis to the right in the lower dorsal region. The erector spinæ muscles are weak and slightly atrophied. The muscles of the upper limbs show no abnormality and all arm reflexes are equal on the two sides. There is pronounced atrophy of both thighs. Circumference measurements: Thighs, right 13 in., left 13½ in., as compared with right calf 15½ in. and left calf 15. Voluntary movement is present, though weak, in the atrophied muscles; they are not unduly atonic, nor has any fibrillation been observed. All other lower limb muscles are normal. The knee-jerks are very sluggish, the left being slightly greater than the right; the left quadriceps reacts to direct percussion, but not the right. The ankle-jerks are brisk, the left being very slightly greater than the right The abdominal reflexes are normal and equal and the plantars flexor. There is no abnormality of sensation, but patient is slightly unsteady in the Romberg position. To faradism all the thigh muscles react fairly well and in proportion to the amount of muscle present. There are no joint lesions in the hips or knees. The heart and lungs are normal, pulse 86, arteries slightly thickened and systolic blood-pressure 140 mm. The retinal vessels show arterio-sclerotic changes. Some varicose veins are present in the lower limbs. X-ray examination reveals some atrophic decalcification at the lower end of both femurs, but no arthritic lesions in hips, knees, or spine. The blood yields a negative Wassermann reaction and the cerebro-spinal fluid is normal with negative Wassermann reaction.

Dr. WORSTER-DROUGHT said that the distribution of the muscular atrophy was somewhat unusual. A so-called "reflex muscular atrophy" secondary to arthritis of the hip or knee-joints was excluded by the clinical and X-ray examination. The distribution, the absence of fibrillary tremors, the retention

of the knee-jerks, the fairly good voluntary movement and the faradic reactions were against a diagnosis of progressive muscular atrophy. Also, in spite of the history of some pain, the perfect retention of sensation and the electrical reactions rendered a post-neuritic atrophy unlikely. The condition, therefore, appeared to be a primary muscular dystrophy of unusual type—what might be termed a "proximal myopathy."

Cases of Epilepsy, General Paralysis and Disseminted Sclerosis, to illustrate Speech Defects.

By Dr. E. W. Scripture.

The speech of patients with nervous diseases is registered on a revolving drum. The records are analysed and measured under a microscope. The following law has been established: Each nervous disease that affects the speech mechanism gives a curve of speech that is pathognomonic for that disease. No two diseases give the same speech curve unless they involve exactly the same nervous mechanism. No disease changes its speech curve except as it progresses or regresses. This is the fundamental law of speech neurology.

Inscriptions of idiopathic epileptics at all times reveal an abnormality that has been found in no other disease and in no normal condition. This is a stiffness of the speech melody without monotony. The peculiarity can be detected otherwise only by the trained ear. It cannot be imitated. Many cases diagnosed as epileptic have been found to be hysterical, and vice versa. Study of the character of the inscriptions leads to the conclusion that idiopathic epilepsy is a congenital form of character, the fundamental feature of which is a diminished adaptability to the whole environment. The researches do not furnish information as to whether the defect is due to abnormality in the psyche, the nervous mechanism, metabolism or the hormone balance. The peculiar stiffness of the epileptic speech melody is so marked that the ear can be trained to detect it. Fifteen years of experience have shown that this stiffness of melody without monotony is the most reliable—perhaps the only reliable—diagnostic sign of the disease.

The trained ear can detect another characteristic always present in the epileptic voice—namely a peculiar hollowness of tone. It is not yet known just what produces this, whether it is special to epilepsy or what it means. Observations with the laryngo-stroboscope may solve the problem.

General paralysis registers in its very earliest stages—even when no speech defect can be detected by the ear and when the diagnosis is doubtful—a specific speech defect known as asaphia. In normal speech the same sounds are repeated not exactly alike but with the degree of precision learned and maintained as proper by the individual. For example, the intervals during which the lips are closed in repeating *pa-pa-pa* do not vary normally from their average by more than 5 per cent. to 15 per cent. In paralytics they vary from 25 per cent. upward to 100 per cent., 200 per cent., and more, without

limit, as the disease progresses. During treatment by malaria the figure gradually sinks till, if the cure is complete, it becomes normal again. This percentage of asaphia varies inversely with the person's degree of development of the sense of conformity, or the social sense. In a paralytic it measures his loss of the social sense.

In the inscriptions of disseminated sclerosis there always appear (except in the few flaccid cases) two or three irregular waves in vowel records. Such waves have never been found in any other disease. They are the result of crico-thyroid and thyro-arytenoid ataxia. The phenomenon is so minute in early cases that nothing can be detected by the ear. The diagnosis, however, is made automatically the moment the inscription is examined with a magnifier. The quite ordinary mistake of diagnosing this disease in its early stages as hysteria is instantly corrected by a speech inscription.

The speech abnormalities have been found to result from a disturbed interaction of three biological factors: (1) An impulse to speak as the person has been taught; (2) a force that hinders the result; and (3) an effort to correct the defect. For example, the impulse to precision in speech, eusaphia, is opposed by antisaphia, with an attempt at correction by anasaphia. Asaphia beyond 15 per cent. in the case described above is due to weakness of the first $\frac{\text{or}}{\text{and}}$ the third, or increased strength of the second. Every other speech phenomenon is the result of the same three factors. Ataxia is the result of the increased antitaxia or weakened eutaxia $\frac{\text{or}}{\text{and}}$ anataxia. The hypertonic speech of spastic conditions is the result of pathologically increased tonus (hypertonia) or weakened eutonia $\frac{\text{or}}{\text{and}}$ anatonia. It is thus possible as the result of an analysis to express a speech condition as an equation. For example, all the speech signs of disseminated sclerosis are the result of eutaxia + antitaxia + anataxia + eutonia + hypertonia + anatonia. This formula, moreover, sums up the entire symptomatology of disseminated sclerosis and may be regarded as the equation of the disease. With such precise analyses available it is quite out of place to use such misleading and largely erroneous terms as "scanning speech," "staccato speech," &c.

Case of Syringomyelia (Morvan's Type).

By Dr. Lewis Yealland.

G. S., barman, aged 49. There is nothing significant in his personal or his family history. Thirteen years ago, painless whitlows occurred successively, over a period of two years, in the little, ring, index fingers and thumb of the right hand. Two months ago he was admitted complaining of dragging and stiffness of the lower limbs and of "always getting sores on the right hand," which were painless but difficult to heal. On examination he presents a spastic paraplegia, not severe enough to prevent his walking without support; scoliosis; and an enlarged, scarred, deformed and discoloured right hand. There are lateral nystagmoid movements and weakness of the right side of the face. There is

slight wasting of the dorsal interossei of both sides, of the right upper limb and more severe wasting of the right shoulder-girdle. Sensations to pin-prick, heat and cold are lost on the right side, over the face, neck, upper limb and thorax as far down as the sixth rib. Sensation to cotton wool is retained over this area. The reflexes are pyramidal in type, including double extensor responses. The sphincters are unaffected. The cerebro-spinal fluid contains a total protein of 0·08 per cent., and no increase in cells.

A Case of Post-encephalitic Respiratory Disorder.

By Dr. MACDONALD CRITCHLEY.

H. B., aged 16, male pupil-teacher, was admitted to the National Hospital for peculiar, frequent attacks of breath-holding.

Patient had an attack of acute epidemic encephalitis in April, 1924; recovery was never complete, a definite inversion of the sleep rhythm having persisted since this illness. In August, 1924, patient developed a persistent short hacking cough without expectoration. Three weeks later, he began to fall down in what were thought to be faints. These turns recurred at very frequent intervals and were present on admission.

Present state.—Patient's attacks consist of recurring spells of inspiratory apnœa going on to cyanosis and mental confusion, followed by forced expiration with a short period of apnœa. Breath then returns in deep, noisy gasps which persist throughout the inter-paroxysmal periods. During the period of apnœa the radial pulse becomes obliterated and the heart sounds are inaudible; a varying degree of mental confusion follows and there may even be a momentary loss of consciousness. The breath-holding is only partly under control, the patient being able voluntarily to inhibit the attacks for a few minutes only. The attacks cease during sleep, and become less marked under hyoscine injections or when the attention is distracted.

Neurological examination.—(1) An inconstant, horizontal, rapid nystagmus on lateral ocular deviation, which is fairly well sustained. (2) Convergence is ill sustained when the fixation point is nearer than four inches to the patient. (3) Marked euphoria with some carelessness in habits and defective sphincter control. (4) Inversion of the sleep rhythm.

Case of Chorea with no Improvement after Eighteen Months' Treatment.

By Dr. W. R. REYNELL.

E. A., aged 47, machinist; choreiform movements of face and limbs, especially right side, since December, 1922. Chorea at age of 12, lasted one year; relapse at age of 18, slight symptoms; second relapse at age of 21, recovered in four weeks; third relapse six months later, from which he has not recovered. Has been six months in hospital during last two years. Sister of patient suffered from chorea and died at age of 11 from heart disease. Father died of phthisis and heart disease.

On examination, weakness of right side, exaggerated tendon reflexes, slight

irregular pyrexia at intervals; slight enlargement of left heart, pre-systolic murmur and thrill.

No improvement has taken place during the last two years in spite of treatment by rest, salicylates, arsenic, chloretone, hyoscine, bromides, &c.

Case of Facial Hemiatrophy.

By Dr. HENRY J. MACBRIDE.

A. D., aged 20. Facial hemiatrophy began at the age of 4, with a "whitish spot" on the right forehead. Fits commenced at the age of 5, and during them she was convulsed generally and unconscious; and when they ceased there was weakness of the left side. She has had other attacks without loss of consciousness; these were accompanied by headache and pain down the left side of the body, with drawing up of the left side of the mouth, left arm and leg.

Reflexes normal and equal on the two sides, except the abdominals, which were weaker on the left side. No objective sensory disturbance made out.

Case of Paraplegia in Scoliosis.

By Dr. JAMES COLLIER.

P. C., female, aged 16. Between the age of 3 and 4 her back commenced to become curved. This curvature gradually became worse, but with the aid of a supporting jacket she has been able to walk comparatively well. Eighteen months ago her legs began to drag, the right preceding the left. Ten months later flexor spasms commenced. Six months ago bladder control became defective. No pain or tight feeling have occurred.

She exhibits very marked scoliosis with severe rotation of the bodies of the mid-dorsal vertebræ. The abdominal muscles are weak; the legs are spastic with brisk knee- and ankle-jerks and extensor plantar responses, upper abdominals just obtainable. Diminution to pin-prick up to seventh and eighth dorsal segments; vibration sense lowered in legs. No tenderness of vertebræ.

X-rays show no evidence of abscess formation nor active disease of the vertebral bodies; marked rotation well demonstrated.

Dr. COLLIER said that there seemed to be little doubt that in this case the scoliosis had resulted from poliomyelitis of the thoracic cord, of which the remarkable weakness of the abdominal muscles was a remaining sign. He submitted that the recent paraplegia was the result of pressure upon the spinal cord from the rotation and deformity of the vertebræ. He (Dr. Collier) had seen four other cases in which severe scoliosis resulting from poliomyelitis had been followed years later by paraplegia from a local lesion of the spinal cord. In the present case the cerebrospinal fluid showed Froin's syndrome, and he suggested that, if this patient did not soon show signs of improvement with rest and extension of the spine, decompression at the site of the lesion was indicated.

Case of Muscular Dystrophy with Pyramidal Signs.

By Dr. REDVERS IRONSIDE.

A. L., female, needlewoman, aged 43. Onset at age of 33 years; difficulty in climbing hills and going upstairs. She has occasionally fallen in the street: unable to pick herself up without help. After over-exertion patient complains of pain in the lumbar and gluteal muscles. She has suffered from "gastritis" since 1910. Patient is an only child; no paternal or maternal relations have suffered from weakness of the limbs or paralysis.

The optic discs, pupils and cranial nerves are normal. Slight difficulty in blowing out the cheeks. No sensory defect. There is wasting of the pectorals, supra- and infra-spinati, and trapezii, and the latissimus dorsi contracts feebly on the two sides. The erector spinæ is flattened on the right side. There is wasting of both lower limbs, more in the right than in the left leg. The right vastus extensor is hypertrophied, both gluteal groups are wasted and the hamstrings are wasted and flattened on the left side. Left hamstring-jerk absent. Both plantar responses extensor, upper abdominal reflexes elicited. The cerebrospinal fluid is normal (protein 0·015 per cent.) and the Wassermann reaction is negative. All muscles of shoulder-girdles, back, buttocks and thighs show partial R.D.

Myopathy of Unusual Distribution.

By Dr. REDVERS IRONSIDE.

G. H., female, aged 27, one of twins. The twin brother is unaffected, as are also three older brothers and two older sisters. The patient at school was never quite able to keep up with the other children in running-games, but not until three years ago was real difficulty noticed in walking and rising from the sitting position. If the patient walks far, she has dull aching sacral pains which do not shoot down the lower limbs. The weakness was felt in the left leg two years before it was apparent in the right.

Points in physical examination: (1) Transverse "quadrangular" smile, and curious soft voice; (2) relatively slight muscular wasting, but great weakness in the ileo-psoas, hamstrings, adductors, gastrocnemii (not soleus) and anterior tibial group; (3) absent ankle-jerks; (4) electrical reactions in gastrocnemii approximating R.D. The gait is waddling. There is no hypertrophy of muscles; no sensory defect. The cerebro-spinal fluid is normal and the Wassermann reaction negative.

Pathological Specimens.

By Dr. W. E. CARNEGIE DICKSON.

(I) *Myxo-chondroma of Base of Skull.*

Florence M., aged 32 (a case of Dr. Macnamara's), had complained of the following symptoms. Vertical headache, occasional vomiting, defective vision, difficulty with speech, numbness of right side of face. The onset of the condi-

tion had occurred about two years previously and the symptoms were steadily becoming worse.

Physical examination showed: Speech slow and slurred: pupils—right greater than left, the right being irregular and reacting neither to light nor for accommodation; lateral nystagmus, with diminished upward movement and convergence of right eye. Both optic discs were blurred at the nasal sides and the veins swollen; anæsthesia of right side of face involving all divisions of fifth nerve; weakness of right masseter and temporal muscles; right side of palate inactive and right vocal cord immobile. Tongue deviated to right on protrusion, with right-sided hemiatrophy. Head held tilted upwards and turned towards right side, while the trunk tended to sway towards the right. Right arm weaker than left, with some inco-ordination. She walked fairly well but with a tendency to sway towards the right. Knee-jerks sluggish and ankle-jerks not elicited. Plantar reflexes flexor, and abdominal reflexes absent. A mass was seen on the right side behind the palate and some glandular swellings were palpable on the right side of the neck. Death occurred in November, 1924.

Post-mortem.—In the base of the skull, and projecting into its cavity, was a large, irregularly rounded, or pear-shaped mass, 2½ in. in transverse, and 2 to 2½ in. in antero-posterior, diameter. It was situated mainly in the region of the sphenoid, expanding and replacing the bone, so that the pituitary gland was displaced and appeared partially embedded on the surface of the tumour, as if "floating" upon it. The prominent growth of the tumour had occurred mainly towards the right, and it extended more than half-way across the middle fossa, and also backwards and to the right, between the foramen magnum and the petrous temporal bone, the apex of which was surrounded by and embedded in the tumour. It had thus encroached extensively upon the cranial cavity, pushing aside and compressing, especially, the right temporo-sphenoidal lobe, the right side of the pons and the middle peduncle and under surface of the cerebellum, the upper part of the medulla being also considerably distorted. The tumour had spread extensively in the substance of the bones of the base of the skull, especially in the body of the sphenoid, the basi-sphenoid and the basi-occipital, and neighbouring parts. It had also spread downwards into and among the tissues on the right side of the neck, being found as a large pseudo-cystic tumour below the right mastoid and behind the ascending ramus of the lower jaw, bulging into the naso-pharynx, and pushing the right tonsil and soft palate downwards and to the left. The contents of this were semi-translucent, very pale, slightly bluish milk-white material of about the consistence of table-jelly.

Microscopically.—The structure appears to be that of an ordinary *myxo-chondroma*, and not that of a chordoma, the mucoid degeneration affecting both cartilage-cells and the fibrous-tissue stroma surrounding the islets of degenerated hyaline cartilage. The large vacuolated cells characteristic of chordoma are not present.

(II) *Hæmangioma of the Mid-brain.*

Hetty P., aged 25, had complained of unsteadiness, "dropping things and difficulty in speaking," for two years. She was admitted under the care of Dr. Harry Campbell, on August 7, 1924, exhibiting slurred and indistinct speech, expressionless face, some limitation in outward movement of both eyes, slight left-sided facial weakness, and occasional antero-posterior tremor of head. Pupils, optic discs and other cranial nerves were normal. There was a constant tremor of the left hand, with dysmetria. The gait was slightly ataxic, but the reflexes were not abnormal. Death occurred on August 31, 1924.

Post-mortem.—The brain, on mesial vertical section, showed, in the region of the mid-brain, just below the lamina and corpora quadrigemina, a dark red *vascular tumour*, $1\frac{3}{4}$ in. in antero-posterior, and about 1 in. or a little more in vertical, diameter, situated in and expanding the crura cerebri and region around the aqueduct of Sylvius, into the upper part of which a horse-hair could be passed for about $\frac{1}{2}$ in., the canal being embedded in the tumour. Anteriorly, the mass extended to within $\frac{1}{4}$ in. of the posterior wall of the third ventricle; whilst, posteriorly, it distorted the upper part of the fourth ventricle, and projected towards the cerebellum, and pushed it backwards. Laterally, it reached the outer surface of the right crus, but, on the left side it did not pass so far beyond the middle line.

The tumour, to the naked eye, consisted of closely aggregated, rounded or irregular vascular spaces, filled with blood, the largest about $\frac{1}{8}$ in. in diameter. Their arrangement was more or less compact, but isolated spaces could be seen around the periphery in the cerebral substance. Some of the spaces show the lighter tint of thrombosis, varying from brick-red to pale white of decolorized thrombus. There was moderate distension of the third and both lateral ventricles, and marked distortion of the anterior part of the roof of the fourth ventricle.

Microscopically.—The structure was that of a *cavernous angioma*, lined by much-flattened cells, presumably endothelial, the framework being composed for the most part of fully-formed dense fibrous tissue. The smallest spaces at the margins had the appearance of dilated capillaries, or capillary-venous spaces, composed of a single layer of flattened endothelial cells, with little or no supporting tissue around them. Various stages of thrombosis, recent to old-standing, were present in many of the spaces, and there were also considerable aggregations of polymorphs in many of them. Hæmorrhage had occurred from some of the spaces, with the presence of numerous phagocytic cells containing blood-pigment.

(III) *Neuro-fibroma of Auditory Nerve.*

Florence G., aged 37, was shown clinically before this Section in December, 1923, by Dr. Worster-Drought, as a case of early tumour of the acoustic nerve.[1] Subsequently, the symptoms and signs gradually increased in intensity, and papillœdema developed in May, 1924. An attempt was made to

[1] *Proc. Royal Soc. Med.*, 1923-24, xvii (Sect. Neurol.), p. 28.

remove the tumour by operation performed in two stages, but the patient died shortly after the second operation.

Post-mortem.—On opening the skull and removing the brain, a tumour about the size of a large walnut was found, lying at the right cerebello-pontine angle, causing considerable flattening and some indentation of the pons, and adhering externally to the petrous temporal bone, around the opening of the internal auditory meatus. Posteriorly, the tumour was broken up and mixed with blood-clot in the operation area. The fifth cranial nerve was stretched antero-posteriorly over the upper aspect of the tumour. The trochlear nerve lay internally, but did not appear to be compressed; whilst the sixth nerve lay internally below, in the angle between the tumour and the pons, and had probably also escaped compression. The upper part of the medulla was slightly pushed towards the left.

Microscopically.—Sections from the posterior part of the tumour, removed at operation, showed it to be a *neuro-fibroma*, composed of irregular whorls and bundles of fibroblasts in some parts, fully formed fibrous tissue in others, the vessels varying from a single layer of endothelium with a narrow zone of supporting connective tissue, up to considerably thickened small arterioles and capillaries, many of the vessels showing various stages of hyaline degeneration. Around some of the vessels there was a moderate amount of small-celled infiltration, and, in their lumina, some excess of polymorphs.

Clinical Meeting at the National Hospital for the Paralysed and Epileptic, Queen Square, Bloomsbury, on Thursday, March 12.

Two Sisters from a Family affected with Dystrophia Myotonica.

By Dr. J. L. BIRLEY.

Family history.—Paternal grandfather, a teacher at Edinburgh University, —healthy, and died of old age. All his children except two, namely, the patient's father and one daughter, died before 50, "most of them of phthisis." Father died, aged 57, of phthisis. In the last few years of his life he had difficulty in relaxing his grasp. He was a marine engineer and had his own business. All his children are in straitened circumstances.

Mother died, aged 62, of phthisis, contracted from her children. She was healthy, and her parents and all her brothers and sisters were healthy and lived to be old. She had eight children:—

(1) Female, died, aged 27, phthisis. Her hands were never developed properly and she could not relax her grasp.

(2) Female—patient, Jennie, aged 45.

(3) Male, died, aged 36, phthisis. Affected like (2), could not open his hands quickly and was always weak.

(4) Male, married, unaffected, childless.

(5) Female, married, unaffected, but her sight is failing owing to developing cataract: has one healthy child.

(6) Female, married, unaffected, childless.

(7) Female, aged 34—Clara, patient; has phthisis. Gives well-marked myotonic reactions.

(8) Male, strong, died aged 19, suddenly, while on parade.

(2) Patient J., aged 45. Complains of difficulty in getting about for twelve years, and difficulty in getting up from chair: has to kneel as she cannot stoop down. Hands are stiff, but she does not complain about them. Recently her legs have felt numb.

Examination incomplete, but she shows the characteristic wasting of face, temporals, neck, forearms and thighs. Myotonia present in flexors of wrist and fingers. Unilateral enlargement of thyroid. Articulation indistinct. Poor mentality. No cataract.

(7) Patient C., aged 34. Four years chronic pulmonary tuberculosis with fibrosis. One year difficulty in walking which is progressive, legs get tired. Never noticed anything wrong with her hands, and regarded as natural her inability to get up from the horizontal position unless she rolled over on her side and pushed herself up with her hands.

Examination: Miserable physique, thin hair, atrophic breasts, normal menstruation. Fibroid phthisis left > right. Small gland right side of neck. Enlargement of right lobe of thyroid. Basal metabolism + 11 per cent. Poor mentality. Vision: right vision $\frac{6}{36}$, corrected $\frac{6}{9}$; left vision $\frac{6}{36}$, corrected $\frac{6}{9}$. Ji in each eye. In each lens, more pronounced in the right eye, numerous extremely fine dust-like opacities are present in the cortex. Expressionless face, wasted temples, narrow high-arched palate, articulation indistinct, voice husky. Profound wasting of neck muscles, especially sterno-mastoids; upper trapezii wasted; head falls about. Musculature of shoulders and upper arms poor and muscles soft; right triceps weak. Wasted forearms, flexors weaker than extensors; myotatic irritability absent in flexors. Intrinsic muscles of hands fairly well preserved; finger movements good. All tendon reflexes in arms obtained with difficulty. Trunk very weak indeed. In the lower limbs the vasti are wasted and the other muscles are fairly normal except that they are soft and in places rather bulky. Moderate weakness of knee extensors and to a less extent of dorsi-flexors. Knee- and ankle-jerks feeble. Plantars flexor. Legs and feet feel numb; vibration is not felt, or at least is grossly diminished, in the upper limbs and everywhere below the level of the third ribs. No other sensory disturbance.

Myotonia is obvious only in the hand grasps, but is demonstrable in frontalis, tongue, deltoids, hypothenar muscles and (?) plantar flexors.

Dr. ADIE pointed out that though there is one child in the succeeding generation it is improbable that she will transmit the condition, as when the disease has reached its full developments in one generation in relation to a common ancestor, it tends to die out and is not transmitted further through the family. It is generally stated that cataracts are present in about one-tenth of

all the cases, but he is of the opinion that if the eyes of all cases were carefully examined by the aid of a slip-lamp changes would be almost invariably found. There were lenticular changes in all the recent cases he has examined by this method.

A Case of Dystrophia Myotonica.

By Dr. J. L. BIRLEY.

Man, aged 39, a clerk in a responsible position.

Family history negative. Father healthy, drowned at sea, aged 50. Mother alive and well, aged 67. One brother aged 43, healthy, with three healthy children. Patient has four healthy children, aged 12 to 1. Both grandparents died aged 85. No history of cataract.

Past history good; always active and fairly athletic. Has had a "weak neck all his life." Four years ago he gave up sculling as he could not hold the oars properly. Three years ago he noticed wasting of the thighs, but he stoutly maintains that although he has occasionally fallen, his legs are not weak, and he frequently walks miles at a stretch. His arms have been getting thinner, but his writing is unaffected; he had recently noticed difficulty in relaxing his grip. No deterioration of vision or of sexual power.

On examination.—An intelligent man of pleasant disposition and cheerful temperament. Characteristic facies: expressionless, all muscles weak and wasted, temporal fossæ hollowed, drooping eyes. No ophthalmoplegia. Articulation defective and modulation poor. No retinal changes. In the peripheral cortex of each lens, especially the right, there are fairly numerous, extremely fine dust-like opacities and several vacuoles. Tongue fissured. All neck muscles profoundly weak and wasted, more particularly the sterno-mastoids. Shoulder-girdle and upper arms show no paresis, but musculature is flabby. Pronounced wasting of forearms, especially extensors, but flexors are much weaker than extensors and have lost their myotatic irritability. Intrinsic hand muscles fairly well preserved with good finger movements. All trunk muscles slightly weak. Musculature of lower limbs is fair with the exception of the quadriceps which is very weak and wasted; the limb cannot be held extended at the knee when raised from the bed. Some weakness of hip extensors. The deep reflexes in both arms and legs, although diminished, are present. Plantars flexor. No sensory disturbance.

Myotonia is obvious in hand-grasps, and can be demonstrated in the wrist extensors and deltoids, but not in the tongue.

Report of Dr. Murray Levick on electrical reactions of facial, neck, forearm, and thigh muscles and deltoids: "No abnormal reaction detected; the response to faradism in some of them is weak, but not more weak than one would expect to find it in muscles that have wasted to that extent. There is no prolongation of the contraction following faradic stimulation of moderate strength after the current has ceased to flow. The response to interrupted galvanic stimulation with metronome interrupter is normal."

X-ray of skull: Very marked enlargement of frontal sinuses. Sella turcica

open widely and rather larger than normal. Chest shows thickening at the lung roots.

Hair on scalp thin, bald in centre. Thyroid small. No obvious endocrine disturbance. Basal metabolism minus 9 per cent.

Hypopituitarism with Retinitis Pigmentosa and Polydactylism.

By Dr. DOUGLAS MCALPINE.

Boy, aged 15 years and 9 months, "always big and fat," at age of 8 years began to have failure of vision which has progressed. In December, 1924, he sustained a fracture of right leg; since then apathetic and apprehensive.

Present history.—Whooping cough and measles in infancy, rheumatic fever at age of 5, no history of fits.

Family history.—Father and mother alive and well; no consanguinity. Two brothers and four sisters alive and well.

General appearance suggests hypopituitarism. Weight 10 st. 13½ lb. Height 5 ft. 9 in. Subcutaneous fat increased in amount in region of breasts, pelvis and hips. Upper and lower limbs have female contour. Well marked eyebrows, scant downy hair on upper lip and limbs; scant axillary hair. Abundant pubic hair with typical feminine distribution. Genitals slightly underdeveloped. Lower jaw recedes: incisors of upper jaw crowded together and inclined backwards.

High narrow palate. Supernumerary digit on each foot; small sessile mass growing from base of fifth digit of left hand.

Vision.—He can only perceive light and hand movements. Retinitis pigmentosa, with changes most marked in the macular regions. Optic discs: arteries small, but otherwise normal.

No evidence of organic disease in central nervous system. Psychical condition: Apathetic; his answers to questions are variable in time and substance, attention poor. No true dementia. X-ray of skull: sella turcica normal in size and appearance. Wassermann reaction (blood) negative. No glycosuria.

Dr. MCALPINE drew attention to the fact that the association of retinitis pigmentosa and polydactyly has already been described, and that symptoms of pituitary disease have also been found in patients with polydactyly. He stated that Dr. R. Batten who examined his case was of the opinion that retinal lesions differed from those of cerebro-macular degeneration.

A Case of Facial Hemiatrophy with Lack of Development of the Breast on the same side.

By Dr. J. P. MARTIN.

The patient is a woman, now aged 20, in whom right-sided facial hemiatrophy commenced at the age of 15. The right breast has never developed, and there is now an absence of subcutaneous tissues on the right side of the chest extending down to the pectoralis major muscle.

A Variant of Charcot-Marie Tooth Disease.

By Dr. J. P. MARTIN.

History.—The patient was well till eighteen months ago, then she suffered from ichthyosis on the forearms. In the spring of 1924 she had four or five fits during a period of about three months: in these fits she became rigid and her head was drawn back; she did not "struggle" and did not lose consciousness.

Soon afterwards her hands began to waste.

The family doctor reports that an elder brother of the patient suffered from a similar disease: his illness began with ichthyosis, then his hands wasted: afterwards his lower limbs became spastic. He was sent to a hospital in Nottingham where he died. A post-mortem examination was held. The doctor was informed that death was due to caries of the cervical vertebræ.

Examination.—Wasting of hands. Slight weakness of dorsiflexion at the right ankle. Otherwise no loss of power. Reflexes all normal. No sensory loss. No changes in cranial nerve functions.

Dr. C. P. SYMONDS said that he had two similar cases under observation with symmetrical wasting of the small muscles of the hands which he regarded as instances of peroneal atrophy. Two years ago he had also shown at a clinical meeting of the Society a patient with similar wasting of the hand muscles who came from a family other members of which were subjects of typical peroneal atrophy.

Dr. BIRLEY also referred to a girl with wasting of the hand muscles only who had brothers affected with peroneal atrophy.

Case of Myoclonus Epilepticus.

By Dr. W. G. WYLLIE.

Henry W., aged 1 year 8 months, has "for several weeks" had attacks of twitching of the limbs, trunk, head and face, almost continuously when awake.

He was born at full term, sat up at 6 months, but makes no attempt to walk, and is backward in speaking.

Family history.—Mother is a very nervous woman. The child's maternal grandmother is in an asylum with dementia and chronic epilepsy. There is one other child, 3 weeks old.

In the attacks there are clonic movements of the arms and fingers, legs, head, eyes and eyelids and lips. Consciousness is usually retained, and the child may continue to smile or to feed himself. In the more severe attacks the child's head gradually sinks down forwards, almost touching his feet, and the eyes assume a vacant look, as seen in petit mal.

Case of Post-encephalitic Myoclonus and Tachypnœa.

By Dr. MACDONALD CRITCHLEY.

E. S., a butcher boy, aged 19. In March, 1914, had an attack of epidemic encephalitis, characterized by insomnia, delirium and myoclonus of the shoulder

muscles. The patient's recovery was never complete; he became dull in mentality. Insomnia gave place to lethargy, and the twitching of the muscles persisted.

His present state is one of mild Parkinsonism. There is definite myoclonus on the upper halves of both trapezii, and to a lesser degree in the pectoralis, deltoid, biceps, and triceps of the left side. The upper bellies of the recti abdominis also show myoclonus. These movements cease during sleep.

The respiration is rapid (40 per minute), and each inspiration synchronizes with the myoclonic jerk. The breathing is noisy, especially during sleep. The tachypnœa, which persists throughout day and night, is not accompanied by any thoracic distress.

Dr. CRITCHLEY referred to the fact that the association of rapid breathing and myoclonus has been also observed by Marie, Hall and others.

Case of Post-encephalitic Contractures and Paroxysmal Tachypnœa.

By Dr. MACDONALD CRITCHLEY.

I. C., female, aged 23. Last June was attacked with acute epidemic encephalitis (diplopia; delirium). Patient has never made a complete recovery from this illness.

Gradual onset of Parkinsonism. Patient states that ever since last June her right hand has been contracted. At present the right hand is claw-like in attitude. Feeble flexion is possible, but extension is impossible. The right elbow is also contracted and cannot be extended past a right angle. The left elbow cannot be extended to more than 120°. Both legs are fixed in extension and the feet are drawn up in an exaggerated pes equinus attitude.

Patient's respiration is normal during the waking state, but when asleep the breathing becomes faster (38 per minute), regular, and shallow.

Dr. BUZZARD pointed out that there were no changes in the muscles themselves that could explain the contractures. When any muscle was fully relaxed its tissue was apparently quite normal to touch, and the muscles were all capable of contracting when not limited by the changes which occurred in or around the joints. In his opinion the condition could be attributed to insufficient care and bad nursing.

Case of Peroneal Muscular Atrophy with Pseudo-hypertrophy and Atrophic Sternomastoids.

By Dr. REDVERS IRONSIDE.

J. G., male, aged 34, single, railway porter. Patient states that at school he was always "short-winded" if he ran far. Six years ago he obtained employment as a porter and has been accustomed to lift 2½ cwt. loads. Four years ago he noticed weakness and wasting in the left ankle, and the left foot dropped. Eight months afterwards he noticed "quivering" of the calf muscles of the left leg. Gradually the weakness has spread to the right leg; since the wasting has been present both feet became blue and cold with a

subjective sensation of pins and needles. One year before the patient first noticed the wasting he sprained his left ankle and was in bed for eleven days. At the age of 9 years had a tubercular adenitis. No family history of similar disease ascertained; his parents were first cousins.

On examination: (1) Cyanosed and wasted "champagne bottle calves," wasted thighs and wasting of the small muscles of both hands; (2) Atrophic sterno-mastoids, especially the sternal heads; (3) Pseudo-hypertrophy in vastus internus on the two sides; (4) Slight involvement of the lower facial musculature (patient cannot blow out his cheeks): (5) Absent ankle-jerks. Sensibility to vibration diminished over tibial malleoli. The abdominal reflexes are brisk and the plantar responses are flexor. In the lower limbs weakness and wasting effect the calf muscles generally, the adductors of the thighs, the glutei slightly, the hamstrings and the ileo-psoas. Gait waddling with slight lordosis. In rising from the extended position on the floor patient tends to climb up his thighs. Intensely marked condition of medullated nerve fibres in both optic discs.

A Case with Epileptiform Seizures.

By Dr. C. P. SYMONDS.

Male, aged 25. In 1922 he began to have occasional epileptic attacks. These gradually increased in frequency and severity. In 1923 paroxysmal headaches commenced associated with nausea. The fits were now sometimes preceded by left-sided paraesthesiæ. Occasionally he had dreamy states with visual hallucinations.

Condition in June, 1924.—Optic discs pale but not swollen. Visual acuity 6/6 both eyes. Slight weakness left palate and right tongue. Tendon-jerks brisker in left upper and lower limbs than right. Wassermann reaction negative in blood and cerebro-spinal fluid (twice examined). Cerebro-spinal fluid twice examined showed (1) cells 45, protein 0·09 per cent.; (2) cells 51, protein 0·16 per cent.; colloidal benzoin curve 2.2.2.2.2. (paretic curve). X-ray of skull showed large sella turcica, sutures rather wide, some dimpling in frontal region.

Treated as for syphilis during next three months with mercury, iodides, and intravenous N.A.B. Continued to have headaches and occasional fits.

Condition in October, 1924.—Increased pallor of optic discs with haziness of edges. General constriction of visual fields. Condition otherwise unchanged. November 6 to 8: given six applications of deep X-rays to region of inter-peduncular space. These caused severe headaches and an increase in the number of fits.

Condition in March, 1925.—During the past four months has averaged one fit a week. Has occasionally had an aura of tingling in *right* face. Mental condition dull. Slight proptosis. Optic discs pale and edges indistinct. Visual fields unchanged. Weakness right face, left palate, left grip. Left knee- and ankle-jerks brisker than right. Wassermann reaction negative in blood and cerebro-spinal fluid. Cerebro-spinal fluid shows cells 9, all lymphocytes,

protein 0·1 per cent., chlorides 0·75 per cent., sugar present, benzoin curve 2.2.2 2.1.

The duration and variability of the symptoms suggested an inflammatory lesion rather than a cerebral tumour. A feature of special interest in the case was the presence of a paretic curve to the colloidal benzoin reaction. Though he had had a large amount of experience in this reaction, he had found a paretic curve only in syphilis, with the exception of one case of tuberculous meningitis and one case of polyneuritis.

He originally regarded the condition as one of cerebral syphilis, but the negative Wassermann reaction and the failure of antisyphilitic treatment to give relief seemed to exclude this diagnosis. He now considered the possibility of some chronic parasitic infection of the nervous system.

Dr. McBRIDE drew attention to the presence of nystagmus which, with the history of diplopia and staggering gait, suggested the diagnosis of disseminated sclerosis. Further, an excess of cells and a paretic curve to the colloidal benzoin reaction were sometimes found in this disease. He inquired as to the nature of the cells present.

Dr. SYMONDS, in reply, stated that the cells in the cerebro-spinal fluid were all lymphocytes; he had not previously observed nystagmus, and the state of the optic discs and of the visual fields was not in favour of the diagnosis of disseminated sclerosis.

Quadriplegia : Showing well-marked Postural Tonus.

By Dr. PHILIP CLOAKE.

J. C., aged 39. Printing-machine minder. Good health, except for dysentery in the Army, until March, 1920, when he developed paralysis of extensors of the fourth and fifth digits of his left hand and pain in his left arm.

May, 1920, sudden paresis and stiffness of left leg and a few days later of left arm. June, 1920, right arm similarly affected, very sudden onset. February, 1921, attacks of pain running up the spine with choking sensation and extreme flexion of the legs, lasting for 30 seconds and terminated by change of position. No loss of consciousness. In December, 1924, the right leg became stiff and weak.

He has had several courses of injections of N.A.B. without material improvement.

Mental state somewhat unduly emotional. Cranial nerves normal except exophthalmos of left eye; exaggerated jaw-jerk. Well marked scoliosis, probably arising during this illness. Weakness of flexion of the head on trunk. No loss of sensation. Abdominal reflexes absent. Moderate increase of postural tonus in the arms, more in the right than left, and more in triceps than biceps and in flexors of wrist than extensors. Lengthening and shortening reactions present. Double drop-wrist and slight wasting of wrist extensors. Power at shoulder quite good. Flexion of elbow much stronger than extension. Grips weak, the right more so than the left. Pronation very feeble, especially on the left. Gripping with either hand causes extension of the other three

limbs, and also adduction and pronation of the other arm. Voluntary movements at the elbow and wrist cause associated symmetrical movements in opposite arm. Yawning produces extension of arms and fingers. Tonic neck influences not apparent. Supinator, biceps- and triceps-jerks brisk on both sides. Stimulation of palm causes extension and adduction of thumb.

Marked increase of postural and contractile tonus in all muscles of the lower limbs. Paresis in extension, left weaker than right. Progressive and spontaneous shortening of extensors of knees when passively flexed. Flexion of knees is associated with flexion and pronation of arms. Marked shortening reaction in quadriceps on eliciting the knee-jerks, with steady increase of contractile tone until complete extension is reached. Plantar reflexes extensor. No flexion reflex. Hyperæsthesia of soles with impaired vibration sense in legs. Bladder unaffected. Constipation marked.

Wassermann reaction positive in the blood and cerebro-spinal fluid; in the fluid globulin increase protein 0·1 per cent., and cells 7 per cubic millimetre.

Five Cases exhibiting Involuntary Movements.

By S. A. Kinnier Wilson.

(1) Senile Chorea.

Female, aged 87. In 1913 involuntary movements of right arm commenced. They have progressively increased in range and intensity, and have spread to all four limbs. Mentally she remains as acute as when seen in 1920. No other member of family affected. Movements are choreic in nature and are most marked in the right arm and leg. Plantars flexor.

(2) ? Epilepsy Partialis Continua.

Male, aged 53. Eighteen months ago the little finger of left hand tended "to get in the way." Six months later tremor of finger movements and power in left hand became weak. Occasional spontaneous pain in fingers and knuckles. Left hand held in exaggerated accoucheur's position with thumb well abducted. Tone increased. Marked irregular tremor of fingers. Antagonists and agonists contract simultaneously and separately. Left face has less expression than right. Plantars flexor. No sensory change.

(3) ? Epilepsy Partialis Continua.

Female, aged 42. Eighteen months ago left hand suddenly became weak. Twelve months ago on examination hand flexed at wrist and fingers extended at metacarpal-carpal joints with œdema of back of hand. No tremor. Six months ago practically no voluntary movement possible in left hand. Slight apparently regular tremor of fingers which has been gradually progressive has arisen in last six months. No other physical sign in central nervous system.

(4) Progressive Lenticular Degeneration.

Female, aged 25. Two and a half years ago tremor of left leg and right arm commenced, gradually progressing to other limbs. No history of acute

illness. No history of jaundice. Sweating of face — marked emotional instability. Voice monotonous. No difficulty in swallowing. Ocular movements good. Tends to keep mouth open. Constant involuntary movements of arms and legs. Reflexes normal. Plantars flexor. Liver function tests show deficiency. No pigmentation of cornea. No family history of similar trouble.

(5) TREMOR. ? NATURE.

Male, aged 69. Twelve years ago patient noticed tremor of hands in volitional movement. This gradually progressed and now involves jaw. At rest no tremor of hands; on voluntary movement tremor of hands of paralysis agitans type. No rigidity of arms. No Parkinsonian stance. No immobility of face. Plantars both doubtful extensor. Knee-jerks very active. Wassermann negative. No sensory disturbance.

See-saw Movements of Eyelids.

By Dr. JAMES COLLIER.

Female, aged 4. Since birth mother has noticed peculiarity of eyes.

On examination right pupil is small and inactive to light. Left average size and reacts well to light and on accommodation. On deviation of eyes to right, right eyelid closes; deviation to left, right eyelid opens. No upward or downward movement of right eye. Perfect movement of left eye. Wassermann reaction negative.

A Case of Myotonia occurring in a Male aged 62 (with Cinematograph Demonstration).

By D. W. J. ADIE and Dr. REDVERS IRONSIDE.

W. W., clerk, aged 62. No family history of the disease can be ascertained and the patient himself has always been healthy and athletic.

Three months ago he noticed constant pins and needles in the hands and arms and feet and legs, and stiffness in the lower limbs on attempting to walk after sitting down or standing still. This stiffness lasted as long as one and a half to two minutes, then he could walk on quite easily.

The march of the disease has been rapid. Two weeks later he noticed difficulty in relaxing his grasp after seizing objects. One week later he began to have a tight feeling round the eyes with inability to open the eyes for a few seconds when he screwed them up tightly.

After gazing at a clock above and to his left he has noticed double vision—he would see the clock with the image of "half a clock" beneath. Soon when he began to speak his voice was like a whisper, but as he went on talking it became normal again. The slightest cough caused a spasm of his thoracic musculature, rendering him completely apnœic with increasing cyanosis lasting forty to sixty seconds. Lately he has had difficulty in opening his jaws after biting food and he is now quite unable to swallow fluids.

When he strains at stool he has painful cramps in his lower abdominal

muscles. He is unable to roll over on his side in bed. These spasms are always induced by voluntary movement, and repetition of the movement makes it easy to perform. There are times when he knows "instinctively" (as he says) that he can perform a movement without its causing a spasm. Sudden movements and contact with cold water freeze, as it were, his limbs into a rigid condition. Since the onset the patient has become self-conscious, emotional and depressed. During the respiratory attacks he feels as if his exitus is approaching.

On examination the muscles generally are well developed and hard, especially the calf muscles. There is no muscular atrophy. Bilateral peripheral opacities are present in the lower and inner quadrants of both lenses. Some degree of spasm is almost constantly present in the face during conversation, causing narrowing of the palpebral fissures, stiffness of the lower face and drawing the corners of his mouth into a "risus." Myotonic phenomena very marked in the limbs, and myotonia in the tongue can be revealed by the dimpling on percussion. The characteristic electrical reactions are present. The reflexes can be elicited. The patient presents besides signs of cardio-renal degeneration. Electro-cardiogram shows left ventricular preponderance. Examination of the larynx shows sluggish movement of the left arytenoid. Pharyngeal and œsophageal delay in swallowing a bismuth meal. Blood and cerebro-spinal fluid calcium normal.

Two Cases of Disseminated Sclerosis with Acute Posterior Column Lesions.

By Dr. C. M. Hinds Howell.

(1) G. T., male, aged 26. Store issuer. Five weeks ago noticed pins and needles in the soles of both feet, spreading of the legs. Ten days later he had pins and needles with numbness and unsteadiness in both hands. The left leg has become stiff and he drags it slightly. No sphincter trouble or diplopia.

On examination there is slight left ptosis. With arms outstretched and eyes shut, wandering "pseudo-athetotic" movements occur. There is slight peripheral loss to light touch and pin prick in hands and feet. Sense of passive movement in joints absent in the fingers, elicited in the toes. Osseous sensibility to vibration absent in both radial styloids, diminished over the left tibial malleolus. There is astereognosis in both hands. The left plantar response is extensor.

(2) S. G., male, aged 19, clerk. Seven weeks ago noticed numbness in the feet and in the ring finger of the left hand, with dragging gait for a few days. Two weeks later his handwriting commenced to alter, became clumsy, and he felt numbness in both hands.

On examination there is slight peripheral loss to light touch and pin prick in both hands. Sense of passive movement in joints absent in the fingers, elicited normally in the toes. Osseous sensibility to vibration diminished over the radial styloids, slightly diminished over both tibial malleoli. Complete astereognosis in the palms of both hands. With arms outstretched and eyes

shut, both upper limbs wander in space. Marked sensory ataxia of both upper limbs.

Dr. Howell pointed out that the symptoms of these cases indicated acute lesions of the posterior columns of the spinal cord which have recovered rapidly, but lately symptoms developed that pointed to the diagnosis of disseminated sclerosis.

Case of Upper Brachial Plexus Root Lesion.

Shown for Dr. C. M. HINDS HOWELL by Dr. REDVERS IRONSIDE.

A. M., male, aged 60 years. Innkeeper.

Four weeks ago, retiring to bed, patient had occasion to use the water-closet. On rising he fell, and his left arm plunged into the closet, the edge of the pan wedged in his left axilla and grazing his ribs on the left side. He lay there for forty minutes. Next morning his left upper limb was perfectly useless.

On examination of the left upper limb there is paralysis and wasting of the latissimus dorsi, the infraspinatus and subscapular muscles, the deltoid, triceps, and biceps, and pronators of the wrist. There is weakness of the supinator longus and the extensors of the fingers. The flexors of the fingers are less affected. Slight wasting of the first dorsal interosseous space. The intrinsic muscles of the hand function well except the abductor of the thumb. Patient grasps the observer's hand by flexing the wrist to a right angle with slight ulnar deviation of the hand.

No sensory loss apart from slight relative impairment of superficial sensation over C 5 and 6 root areas. The affected muscles react to direct percussions of and show partial R.D. Plantar responses are flexor.

Notices of Recent Publications.

Les Manifestations tardives de l'Encéphalite épidémique. By Gabrielle Lévy. Paris: Gaston Dain. 1925.

This contribution to the vast literature of encephalitis is based upon a study of some 129 cases under the author's personal observation, which showed various late manifestations. It comprises a careful clinical study of the symptomatology in addition to chapters on prognosis, pathological anatomy, &c. At the outset, the author distinguishes true post-encephalitic sequelæ from residual phenomena which have survived from the acute phase. The various manifestations are dealt with under the following headings: (1) *Excito-motor phenomena* (chorea, bradykinesia, myoclonus—including hiccough, and isolated tremors); (2) the *Parkinsonian syndrome*; and (3) various other disturbances comprising: (a) *neurological* (torsion spasm, hemiplegia, sensory disturbances, ocular signs); (b) *general* (respiratory, sleep, temperature, circulatory and nutritional); and (c) *psychic*. Descriptions of the excito-motor and Parkinsonian phenomena are carefully detailed; the section on ocular manifestations, however, although good, is scarcely complete. The author makes no mention of the jerky character and occasional asynchrony of the eye movements; she states that loss of pupillary reaction to light with preservation of the accommodation reflex (which she terms the "Argyll phenomenon") has not been known to occur except in a large pupil. Beyond stating that squint is rarely a late manifestation, no mention is made of strabismus. Vestibular nerve disorders are, in the author's experience, not infrequent, and the caloric and galvanic tests have given feeble responses. Respiratory disorders are classified in the same manner as in her paper of 1922; this section is preceded by a short bibliography. Disorders of sleep and heat regulation are discussed, and a short description is given of nutritional aberrations, under which title are included obesity, the adiposo-genital syndrome, polyuria and glycosuria. Quoting the work of Ferraro on the basal metabolism in post-encephalitis, the author states that an "amphotonic" condition prevails, wherein both sympathetic and parasympathetic systems are in a state of increased tonus. Chapters 5 and 6 deal with the psychic disturbances in adults and in children. In a brief section on the serological findings, she states that an hyperglycosis in the spinal fluid is frequent, being often associated with a normal blood sugar level. The Bordet-Wassermann reaction gave in several of her cases a positive reaction in the blood, although no other evidence of syphilis could be found in the patients or their relatives. A short chapter deals with the prognosis of the post-encephalitic manifestations, and with the question of the persistence of the virus in the tissues; treatment is not dealt with. A description is given of the pathological

anatomy of four cases; the notes of seventeen of the more interesting cases in the series are appended.

Mlle. Lévy's contribution to the clinical study of these conditions is very complete, and testifies both to a close clinical observation and to an intimate knowledge of the vast literature of the subject. Her short section on the pathogenesis of the symptomatology, however, is meagre and disappointing and does nothing to advance our conceptions of the morbid physiology of post-encephalitis. Thus, she suggests a medullary origin for myoclonus; the Parkinsonian syndrome and chorea are referred to the pallio- and neo-striatum respectively; respiratory and thoracic upsets she regards as either bulbar or mesencephalitic in origin. Whilst recognizing the difficulty in dealing statistically with a condition which is so polymorphic in its manifestations and in which recrudescences and relapses occur, one would have welcomed more numerical data regarding the relative frequency of the various symptoms. The volume concludes with a large bibliography which, though comprising most of the French writers on the subject, omits many well known English and American works. It is a pity that more care has not been expended over the compilation of this section, as most of the references are incomplete; in the majority of instances no page is given. Numerous errors in spelling occur: such as "Britisch," "Brammwell," "Perdee," "Niculescu," "Kiener Wilson," "J-C. Spence." In one reference at least the name of the periodical is omitted, although the date and page are given.

Die Psychoide als Prinzip der organischen Entwicklung. Von E. Bleuler. S. 152. Berlin: J. Springer. 1925. Price 6.60 marks.

This monograph by a well-known psychiatrist is an attempt to contrast the mechanisms which determine the purposefulness of psychical activities with that of those that control other physiological functions and the development of organisms. It is impossible to give here a review of the author's conclusions, but a short note on the lines on which his arguments are developed will serve to indicate the interest the book will have to all interested in the biological aspects of psychology. It is not a new thesis but the manner in which it is dealt with gives it special interest to the psychologist. It is essentially a monistic hypothesis.

The purposefulness of the reactions of the body or its parts, of unicellular organisms as well as of the nervous system and of other organs of multicellular bodies, depends on the fact that accumulated experiences serve as a guide for future activities. Each event influencing an organ leaves behind it a special change in that organ, an engram in Semon's words, so that similar or identical stimuli which later reach that organ will elicit similar or identical reactions. We speak of this persisting change in the conscious mind as "memory," but in this sense memory, i.e., the influence of experience imprinted as engrams on organs or on their ancestors, is not confined to the mind, for analogous influences determine the reactions of other organs of the body which

may be affected by experience. In its simplest state memory in this sense exists in inanimate objects, and there is consequently a continuity of the inanimate, animate and psychical worlds.

It is to the sum of these biological adaptive functions (reflexes and Artenentwichlung) of the body in contrast to those of the mind that Bleuler applies the term "psychoide." The psyche (the cortical mind) is a special development of the original "psychoide."

Proceedings of the Seventh International Congress of Psychology. Pp. 388. Cambridge. 1924. Price 12s. 6d.

This volume contains papers read at the Seventh International Congress of Psychology held at Oxford in 1923, under the Presidency of Dr. C. S. Myers, who is responsible for editing the volume. Notices of many of the papers have already been published, but their collection in complete form, under the careful editing of the President, will be welcomed. No discussions are included in this volume.

The letterpress and the editing attain the high standard to be expected from the Press which is responsible for its publication.

Social Aspects of Psycho-Analysis. Edited by ERNEST JONES. Pp. 240. London: Williams and Norgate. 1924. Price 7s. 6d.

This volume contains a series of lectures delivered before the Sociological Society by members of the British Psycho-Analytical Society, outside the ranks of which it is claimed no trained analysts exist in England. The titles of the lectures indicate sufficiently the nature of the volume; Dr. Ernest Jones on "The Relationship of Psycho-Analysis to Sociology"; Dr. Glover on "Man the Individual"; Mr. Flügel on "The Family"; Dr. Eder on "Psycho-Analysis in Relation to Politics." Miss Barbara Low on its bearing on "Education," and Miss Sharpe on "Vocation." The book contains nothing new, but is a simple presentation of psycho-analytical views. Sexual factors still claim a prime importance in the determination of human conduct.

Dynamic Psychology. An Introduction to Modern Psychological Theory and Practice. By Dom T. V. MOORE. Pp. 439. London: J. B. Lippincott Company. 1925. Price 15s.

This book by the Director of the Clinic for Mental and Nervous Diseases in the Province Hospital, Washington, who is also a member of the Order of St. Benedict, aims at giving an insight into the modern trends of psychology, and at the same time serving as a practical introduction to the clinical problems of the understanding and treatment of borderline mental diseases. This application of psychology to pathological states is one of the dominant features of the book. The author's views are, on the whole, rational and practical, though perhaps not distinguished by depth or originality, and certainly give his volume a considerable value to the student whose knowledge

of psychology is limited and whose clinical experience is small. As the book is intended to appeal to a wide class of readers many of its pages are filled by a discussion of elementary physiological facts and theories, the recapitulation of which is scarcely necessary for medical students or practitioners. Some chapters are devoted to rather cursory but impartial reviews of the work of Freud and his followers, by whom the author is considerably influenced. Its most interesting pages are perhaps those in which the author expresses his personal views on the points of contact between psychology and philosophy.

The book is admirably written and the presentation of its subject matter is as simple and direct.

Étude anatomique du Système nerveux central d'un Chien dont le Pallium a été enlevé. By Dr. ARMANDO FERRARO. Pp. 102. Utrecht: Imprimerie Zuidam. 1924.

This interesting anatomical study was made in Winkler's laboratory on the central nervous system of a dog from which Zeliony had removed the whole of the pallium; the animal lived for four years after the operation. Zeliony and Pawlow have already dealt with the physiological observations made on the animal.

Microscopical examination has shown that the whole neopallium was removed, with exception of a small part of the gyrus fornicatus and of the limbic areas, while of the paleopallium only parts of the anterior and posterior olfactory lobes of the lobus paraolfactorius and of the pyriform lobes remained. The caudate nucleus was damaged on both sides, but unequally, the putamen even more so, while the globus pallidus was well preserved on the one side and little injured on the other. The material was therefore in many respects similar to that investigated by Holmes and Rothmann. Its study, which was undertaken in sections stained to demonstrate both myelinated fibres and nerve cells, has yielded many interesting observations on the anatomy and connections of subcortical organs, which must be studied in the original. Numerous photographs and excellently reproduced drawings illustrate the anatomical descriptions.

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EDITOR.